Cannabis use and mental health

Willemijn van Gastel

Research in this thesis was supported by a TOP grant from the Netherlands Organization for Scientific Research (ZonMW TOP grant no. 91207039) to dr. M.P.M. Boks.

Financial support by the Rudolf Magnus Institute for the publication of this thesis is gratefully acknowledged.

ISBN: 978-94-6191-668-6
Printed by Ipskamp drukkers, Enschede
Lay-out by: Ilse Stronks, Ipskamp Drukkers, Enschede
Cover: Willemijn van Gastel

Cannabis use and mental health

On the relationship of cannabis use with psychiatric symptoms

Cannabisgebruik en de geestelijke gezondheid

Over de relatie van cannabisgebruik met psychiatrische symptomen
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de
rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van
het college voor promoties. In het openbaar te verdedigen
op donderdag 21 maart des ochtends te 10.30 uur

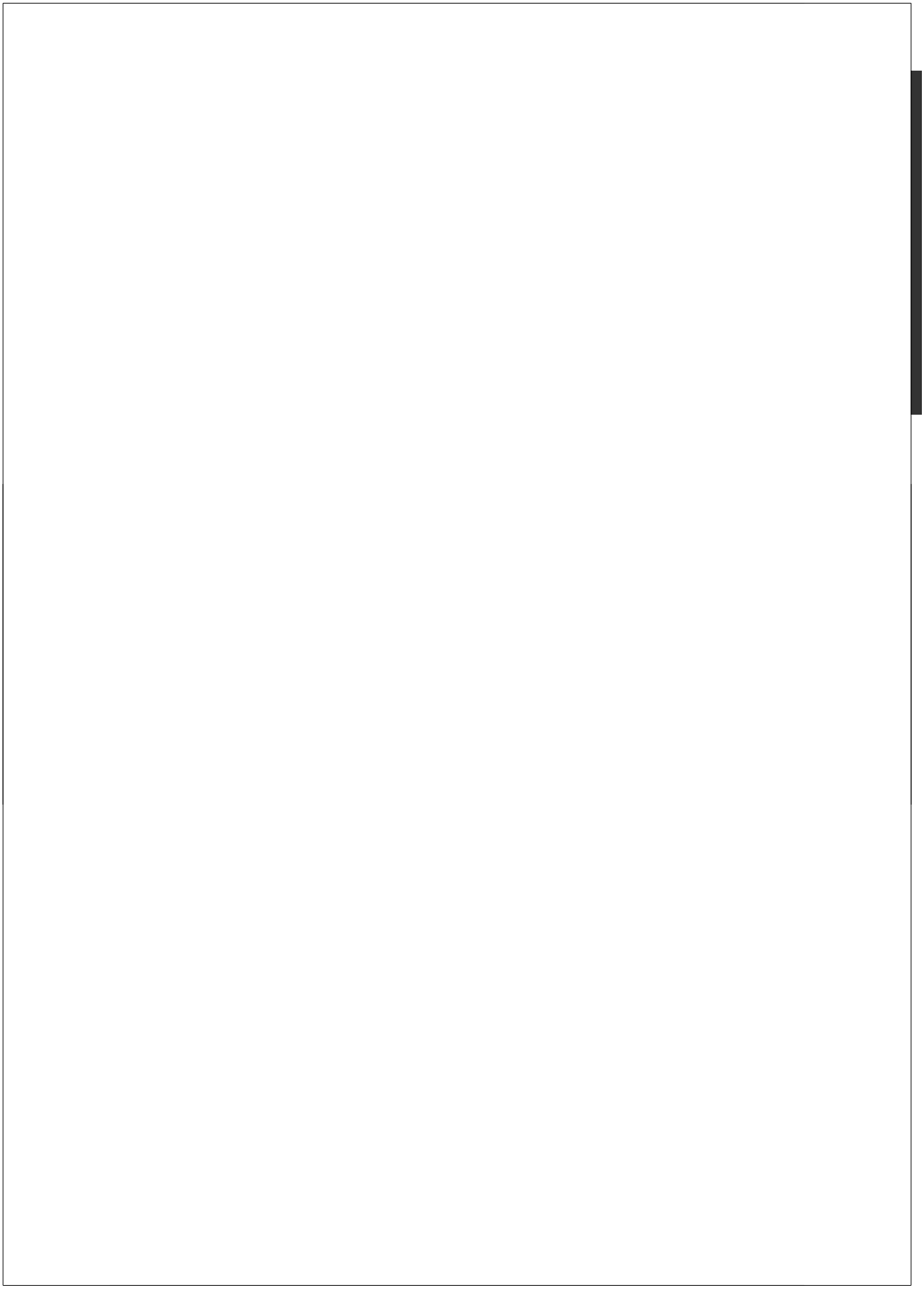
door

Willemijn van Gastel
geboren op 19 april 1985
te Arnhem

Promotor: Prof. dr. R.S. Kahn
Co-promotor: Dr. M.P.M. Boks

Voor Kees & Margreet

TABLE OF CONTENTS



1

General Introduction and outline

"C'est ce que les Orientaux appellent le kief; c'est le bonheur absolu. Ce n'est plus quelque chose de tourbillonnant et de tumultueux. C'est une béatitude calme et immobile. Tous les problèmes philosophiques sont résolus. Toutes les questions ardues contre lesquelles s'escriment les théologiens, et qui font le désespoir de l'humanité raisonnante, sont limpides et claires. Toute contradiction est devenue unité. L'homme est passé dieu."

- Charles Baudelaire on cannabis in *Les Paradis Artificiels* (Baudelaire, 1860)

'This drug is as old as civilization itself. Homer wrote about, as a drug that made men forget their homes, and that turned them into swine. In Persia, a thousand years before Christ, there was a religious and military order founded which was called the Assassins and they derived their name from the drug called hashish which is now known in this country as marihuana. They were noted for their acts of cruelty, and the word "assassin" very aptly describes the drug. (…) *Not long ago we found a 15-year-old boy going insane because, the doctor told the enforcement officers, he thought the boy was smoking marihuana cigarettes.'*

- Harry Anslinger on cannabis, during a hearing for the American House of Representatives on the Marijuana Tax Act (Anslinger, 1937)

Cannabis (also known as Marijuana, Bambalachacha, Hashish, Kaya, Dope, Marimba, Weed, Pot ...) is one of the oldest and most popular mind-altering substances in the world. The earliest archaeological evidence dates back 10,000 years and first records of use of its psycho-active properties to 2,700 BC (Childers and Breivogel, 1998). Nowadays, it is the most popular illicit substance worldwide (European Monitoring Centre for Drugs and Drug Addiction, 2012). Until about 1850, it was mainly seen as a valuable raw material, used for clothing, paper and ship sails and riggings in the Western world. From the moment the psycho-active properties of the cannabis sativa plant became known here, it has evoked extreme reactions: from users who celebrate the mind-altering effects to opposers who condemn it based on moral, political and public mental health accounts.

This thesis aims to provide the debate on cannabis use and mental health with scientific arguments, with a focus on adolescence and young adulthood. This introduction provides some background as to why the relationship of cannabis use with mental health is studied so extensively, and especially during adolescence. The mode of action of cannabis in the brain is shortly introduced as well as the prevalence of cannabis use, putting Dutch cannabis consumption in an international context. Next, studies about the association between cannabis use and mental health are summarized, as well as the evidence for several explanatory mechanisms. Finally, an outline of the studies in this thesis is provided.

CANNABIS IN THE BRAIN

The major psycho-active ingredient of the cannabis sativa plant is Δ-9-tetrahydrocannabinol (THC), with cannabidiol (CBD) and cannabinol (CBN) present in lesser quantities (Childers and Breivogel, 1998). Preparations of dried flowers and subtending leaves and stems of the female cannabis plant are referred to as weed or marihuana. Dutch weed contains particularly high levels of THC, with a mean of 17% over the past five years (Niesink and van Laar, 2012). Hashish refers to concentrated resin from the flowers of the female cannabis plant. Imported hashish is the cannabistype with the highest CBD-level (6.1% on average) on the Dutch market (Niesink and van Laar, 2012).

In mammals, the effects of cannabis are mediated by cannabinoid receptors (CB1 and CB2) (Glass *et al.* 1997; Wilson and Nicoll, 2002). CB1 receptors are widely distributed throughout the brain (Glass *et al.* 1997) whereas CB2 receptors are mainly found in peripheral tissue (Munro *et al.* 1993). These receptors are normally activated by endocannabinoids, endogenous ligands including anandamide and 2-arachidonylglycerol (2-AG)(Childers and Breivogel, 1998). The endocannabinoid system is involved in a range of physiological systems including pain-sensation, mood, appetite and memory (Childers and Breivogel, 1998).

Cannabinoid receptors are primarily found on presynaptic nerve terminals and act to inhibit calcium ion influx and facilitate potassium channels. As a result, stimulation of cannabinoid receptors modulates the action of other neurotransmitters, including GABA, acetylcholine, dopamine and glutamate (Childers and Breivogel, 1998).

The main effects of cannabis on the central nervous system are thought to be primarily due to THC. They include an impaired control of motor movements and posture, reduced short-term memory, disruption of attention mechanisms, altered sensory awareness, analgesia, endocrine regulation, thermoregulation and possibly an immunosuppressive action. The effects are reflective of the distribution of these receptors in the various brain regions associated with these functions (Breivogel and Childers, 1998). Recently, CBD has received more attention of researchers, as there is evidence that this cannabinoid counters the effects of THC and even has *anti*psychotic properties (Morgan and Curran, 2008).

Especially the developing brain appears vulnerable to cannabis use and early use could have an enduring adverse impact (Bossong and Niesink, 2010). This is one of the reasons for the particular focus on adolescents in research on the association between cannabis use and poor mental health. According to the model of Bossong and Niesink (Bossong and Niesink, 2010), adolescent exposure to THC disturbs physiological control of the

endogenous cannabinoid system over glutamate and GABA, interfering with maturation of neural circuitries within the prefrontal cortex. The severity of this impact is dependent of the dose, exact time-window and duration of exposure to cannabis.

CANNABIS USE IN THE NETHERLANDS

Another reason for the specific attention of researchers for adolescents and young adults is that cannabis use is most prevalent among these age groups: in the Netherlands, the percentage of past-year cannabis use among 15-24 year olds (16.1%) is twice that in the age category of 25-44 and even eight times as high as in the age category of 45-64 years. Other factors that are associated with cannabis prevalence are gender and urbanicity. Men use more cannabis: in 2005, 29.1% indicated to have used cannabis at least once in their life whereas 16.1% of women did. Furthermore, of those residing in one of the larger cities of the Netherlands 38.7% indicates recent cannabis use, compared to 4.3% of rural inhabitants (van Laar, 2011).

Research into the putative threat to mental health that cannabis use carries has had an impulse by the steep increase of the percentage of patients in addiction treatment with cannabis-related problems from 11% in 1995 to 30% in 2010. The majority of these patients is male (80%) with a mean age of 28 years (Landelijk Alcohol en Drugs Informatiesysteem, 2011).

Young users

Cannabis use increases with age: in 2011, virtually no children aged 11 or 12 years indicated to have used cannabis (0.3% (van Laar, 2011)); for adolescents aged 16 years this was 20.7%. As in adults, teenage girls use less than their male counterparts: 10.5% of boys aged 12 to 18 years have used cannabis in the past year, versus 4.8% of girls in this age category. Half of adolescents who used cannabis in the past year, did this once or twice in the past month (51%); while 15% used more than ten times in the past month. Although the percentage of adolescents who used cannabis decreased from 19% in 2003 to 11% in 2011 (van Laar, 2011), the number of young cannabis users who receive treatment for cannabis-related mental problems has increased fourfold, from 470 in 2001 to 1,975 in 2010 (Landelijk Alcohol en Drugs Informatiesysteem, 2011).

International comparison

Compared to other European countries, the past-year prevalence of cannabis use for residents between 15 and 64 years of age is average in the Netherlands (7%). The lowest prevalences are found in Portugal (4%) and Greece (2%), the highest in Italy (14%), Spain

(11%) and France (9%). Overseas, prevalence is even higher: 12% for the United States of America (age category 12-99 years), 11% in Canada (age category 15-99 years) and 10% in Australia (age category 14-99 years). For young cannabis users (age 15-16 years), the percentage of users was highest in France (24%), followed by the United States of America (18%), Spain (15%) and the Netherlands (14%) in 2011 (European School Survey Project on Alcohol and Other Drugs, 2012). Although a range of other factors should be considered, this suggests that a repressive policy does not necessarily lead to a lower prevalence.

Cannabis and mental health

Cannabis use has been found to induce transient, and usually mild, psychotic and affective experiences (Isbell *et al.* 1967; Tart, 1970; Thomas, 1996; D'Souza *et al.* 2004). The focus of this thesis lies on the association between cannabis use and enduring (sub)clinical psychiatric symptoms. Since evidence for a relationship tends to accumulate for psychotic symptoms specifically (Moore *et al.* 2007), special attention will be paid to this symptom dimension.

General mental health problems

Adolescent cannabis use, regular or heavy use in particular, has been associated with a range of psychiatric symptoms. Increased rates of externalizing as well as internalizing problems have been reported by young cannabis users, such as delinquent behaviour, conduct disorder and attention problems (Fergusson *et al.* 2002), psychotic symptoms (Arseneault *et al.* 2002), anxiety and depressive symptoms (Degenhardt *et al.* 2003). In particular those who started to use cannabis before the age of 16 years report an elevated rate of symptoms: psychotic symptoms (Arseneault *et al.* 2002; McGrath *et al.* 2010; Schubart *et al.* 2010), adjustment problems including depression, crime and suicidal behaviour (Fergusson *et al.* 2002), anxiety (Hayatbakhsh *et al.* 2007), externalizing behaviour (Hayatbakhsh et al. 2008) and in the cognitive domain attentional dysfunction (Ehrenreich *et al.* 1999), poor educational achievement (Horwood *et al.* 2010) and poor executive functioning (Fontes *et al.* 2011). The risk increases with higher frequency and longer duration of use for psychotic symptoms (Arseneault *et al.* 2002; Monshouwer *et al.* 2006), depression and anxiety (Fergusson *et al.* 2002; Patton *et al.* 2002); (Degenhardt *et al.* 2003; Hayatbakhsh *et al.* 2008) and adjustment problems (Fergusson *et al.* 2002). Especially the combination of heavy use and young age at onset is associated with a high risk for psychiatric disorders (Schubart *et al.* 2010; Rubino *et al.* 2012).

Less is known about the relationship between cannabis use and general mental health, and which characteristics influence this relationship. The term 'general mental health' in this thesis broadly refers to psychosocial functioning. This includes for example mood and emotional problems, somatic complaints, obsessive-compulsive behaviour, anxiety,

sleep problems, hyperactivity, paranoia and social functioning. More knowledge on the association with cannabis use in the general population is important, since this is where the focus of public mental health strategies lies. A comprehensive measure of general mental health in this type of research facilitates concise screening and early detection of symptoms.

Psychotic symptoms

Schizophrenia is the most well-known psychotic disorder, with an estimated lifetime prevalence of 0.5-1% worldwide (McGrath *et al.* 2004). Combined with other psychotic disorders, such as schizo-affective and schizophreniform disorder, the lifetime prevalence has been estimated at 2-3% (Perala *et al.* 2007). The correlated symptom-dimensions underlying psychotic disorders (termed 'the psychotic syndrome' in a review by van Os and colleagues (van Os *et al.* 2010)) are *psychosis* (hallucinations and delusions – 'positive' symptoms), *motivational impairment* (avolition, amotivation – 'negative' symptoms), *affective dysregulation* (depression, mania) and *alterations in information processing* (cognitive impairment) (van Os *et al.* 2010). The term 'psychotic-like experiences' refers to subclinical psychotic symptoms occurring in the general population. These experiences distinguish themselves from clinical psychotic symptoms in that they are not associated with severe distress or an experienced need for care. Although psychotic-like experiences are normally transient in nature (Dhossche *et al.* 2002; Hanssen *et al.* 2005; Wiles *et al.* 2006; Dominguez *et al.* 2011; Wigman *et al.* 2011), they can persist and are predictive of clinical psychosis (Kelleher and Cannon, 2011; Poulton *et al.* 2000).

Cannabis use has been implicated as a risk factor for psychotic symptoms in particular, ranging from subclinical psychotic-like experiences to clinically defined schizophrenia (Andreasson *et al.* 1987; Arseneault *et al.* 2002; van Os *et al.* 2002; Fergusson *et al.* 2003; Henquet *et al.* 2005; Moore *et al.* 2007). Cannabis-using patients have a younger age at onset of symptoms (Large *et al.* 2011) and cannabis use may exacerbate symptoms in patients with established psychosis (Mullin et al. 2012). Furthermore, cannabis use has been hypothesized to be one of the major risk factors causing persistence of subclinical symptoms, and even transition into florid psychosis (Van Os *et al.* 2002; Moore *et al.* 2007; Kuepper *et al.* 2011; Large *et al.* 2011) .

The risk of psychotic symptoms and psychotic-like experiences has been found to increase with frequency and duration of cannabis use (Arseneault *et al.* 2002). Furthermore, the risk has been suggested to increase when cannabis is used at an early age, before 15 years; based on cohort studies (Arseneault *et al.* 2002; McGrath *et al.* 2010) and neurobiological findings (Bossong and Niesink, 2010).

The nature of the association

One of the reasons that cannabis use has been studied so extensively as a risk factor for mental health problems, is that it is one of the few factors that may be liable to prevention. Policies and public (mental) health strategies have aimed at diminishing cannabis use for decades. For such strategies to be of avail in terms of public health gain (e.g. lower prevalences, subjective burden and government expenses on mental health care institutions), the nature of the association is of cardinal importance. Intuitively, one could think that data linking cannabis use to mental health problems automatically indicate that cannabis use is a cause of these problems, and so that quitting cannabis use would diminish these problems. Unfortunately, the truth of the matter is more complicated. Instead of a cause, cannabis might well be the result of either mental health problems or a proneness thereto. Alternatively, both a mental vulnerability and cannabis use could be the result of other risk factors, in other words: the association between both could be confounded by other factors.

Cannabis use as a cause

First, cannabis use could be a (component) cause of mental health complaints. Evidence for adverse causal effects on mental health has mainly centered on psychotic symptoms and schizophrenia. Several cohort-studies report cannabis use preceding the onset of psychotic symptoms (Andreasson *et al.* 1987; Arseneault *et al.* 2002; van Os *et al.* 2002; Fergusson *et al.* 2003; Henquet *et al.* 2005). Proposed mechanisms underlying this supposed causal relationship between cannabis use and psychotic symptoms include persistence of normally transient subclinical symptoms (Cougnard *et al.* 2007), an adverse impact on the endo-cannabinoid system of the developing brain, interfering in the maturation of neural circuitries in prefrontal regions (Bossong and Niesink, 2010) and an interaction with a variation within the catechol-methyl-transferase (COMT) gene (Caspi *et al.* 2005; Henquet *et al.* 2006; Costas *et al.* 2011) or the AKT1-gene (Van Winkel *et al.*, 2011; Boks, 2012; Decoster *et* al., 2012; DiForti *et al.* 2012). This implicates that particularly people carrying a specific genetic variation are at greater risk of developing psychotic symptoms when they use cannabis.

Several studies have found support for a causal role of cannabis use in other mental health problems as well, including anxiety and depression, crime and suicidal behavior (Fergusson *et al.* 2002; Patton *et al.* 2002; Degenhardt *et al.* 2003; Hayatbakhsh *et al.* 2007). Although a dose-response relationship, in the form of a stronger association for an earlier age at onset, high frequency or long duration of use, is consistent with a causal relationship, it does not necessarily indicate one (Macleod *et al.* 2002; Macleod *et al.* 2004; Smith *et al.* 1992).

Cannabis use as a result

Second, there could be a causal relationship in the opposite direction, with (a vulnerability to) mental health problems leading to cannabis use. Adolescents suffering from early (subclinical) signs of mental health problems may use cannabis in an attempt to self-medicate (Henquet *et al.* 2005; Macleod *et al.* 2007). This hypothesis is supported by literature for conduct disorder (Fergusson *et al.* 1993; Pedersen *et al.* 2001), ADHD (albeit with a less strong association for cannabis than for smoking and alcohol use) (Charach *et al.* 2011) and mood- and anxiety disorders (Buckner et al. 2007; Fox et al. 2011; Wittchen et al. 2007; Buckner et al. 2012).

Other risk factors

Third, a common set of risk factors could be causing both cannabis use and mental health complaints (Macleod and Hickman, 2006; Macleod *et al.* 2007). This view is supported by the minimization or even disappearance of the association between cannabis use and mental health problems when other risk factors for poor mental health are accounted for (e.g. Macleod *et al.* 2004; Monshouwer *et al.* 2006).

Socio-demographic factors that might influence both cannabis use and mental health problems, and could thus explain the association altogether, include lower socio-economic status, urbanicity, social support, poor academic achievement, male gender, other substance misuse (particularly tobacco smoking), migration and traumatic experiences (Konings *et al.* 2012; Larsson *et al.* 2012; Monshouwer *et al.* 2006; O'Hare *et al.* 2012; Selten *et al.* 2012; Termorshuizen *et al.* 2012). It is also conceivable that biological factors confound the association – for example, some genetic risk factors for psychosis may also predispose to cannabis use. Confounding by early or genetic factors is supported by the recent finding of smaller orbitofrontal cortex volumes at age 12 years, preceding initiation of cannabis use by age 16 years (Cheetham et al. 2012).

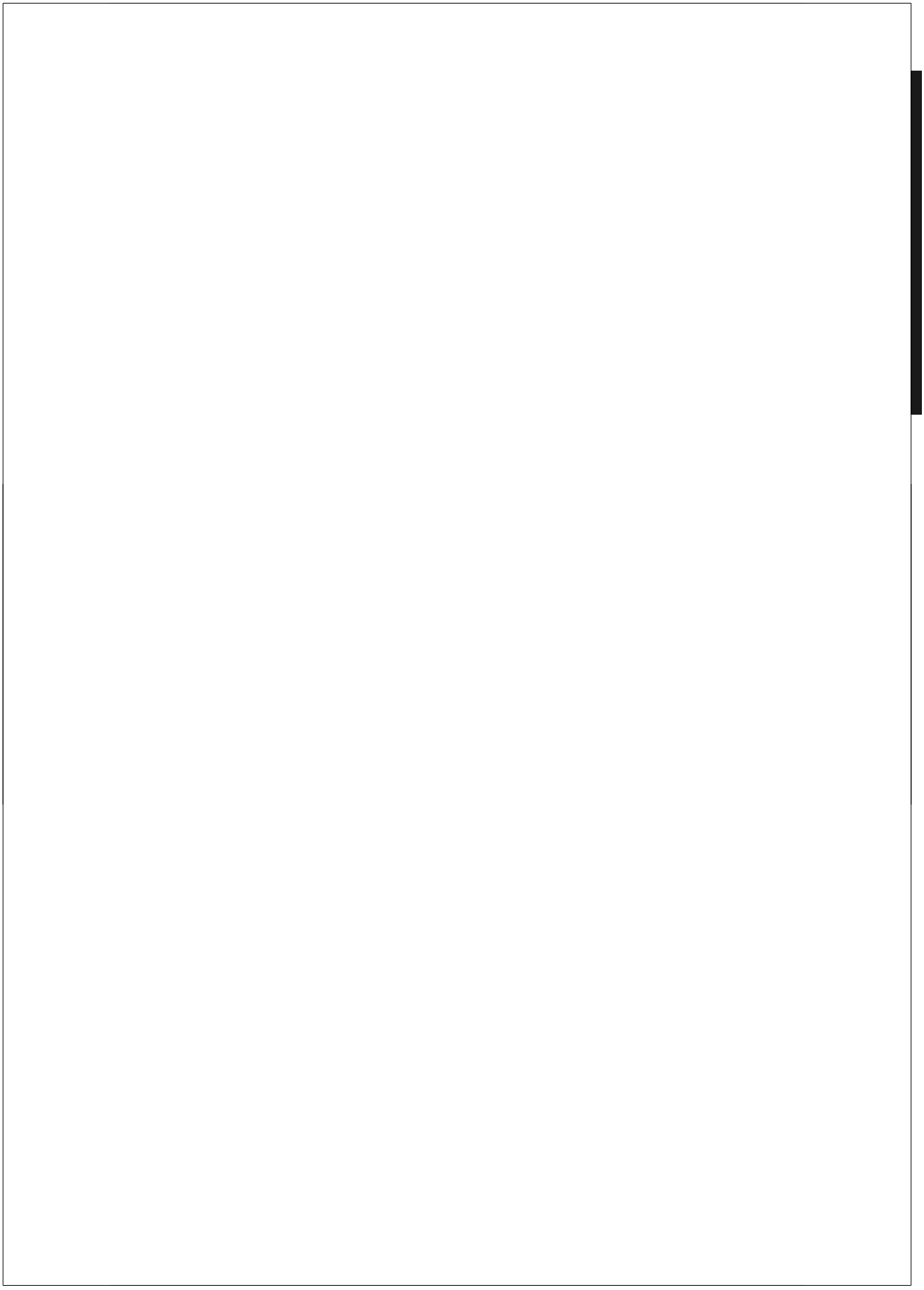
This thesis aimed to further explore the association between cannabis use and mental health, by ascertaining the association itself as well as by investigating the possible underlying mechanisms.

OUTLINE OF THIS THESIS

Part I of this thesis investigates young adolescents, in the age of 12 to 16 years. **Chapter 2** focuses on the association between cannabis use and general mental health problems. The study is cross-sectional in nature, but by comparing risk factors for mental health problems to those for cannabis use itself, it provides insight into the possibility of confounding as an underlying mechanism of previously reported associations. **Chapter 3** investigates the association of cannabis use with positive psychotic experiences. It compares different levels of intensity of use, including a 'discontinued' category, comprising young adolescents who used in the past but had abstained for at least one year.

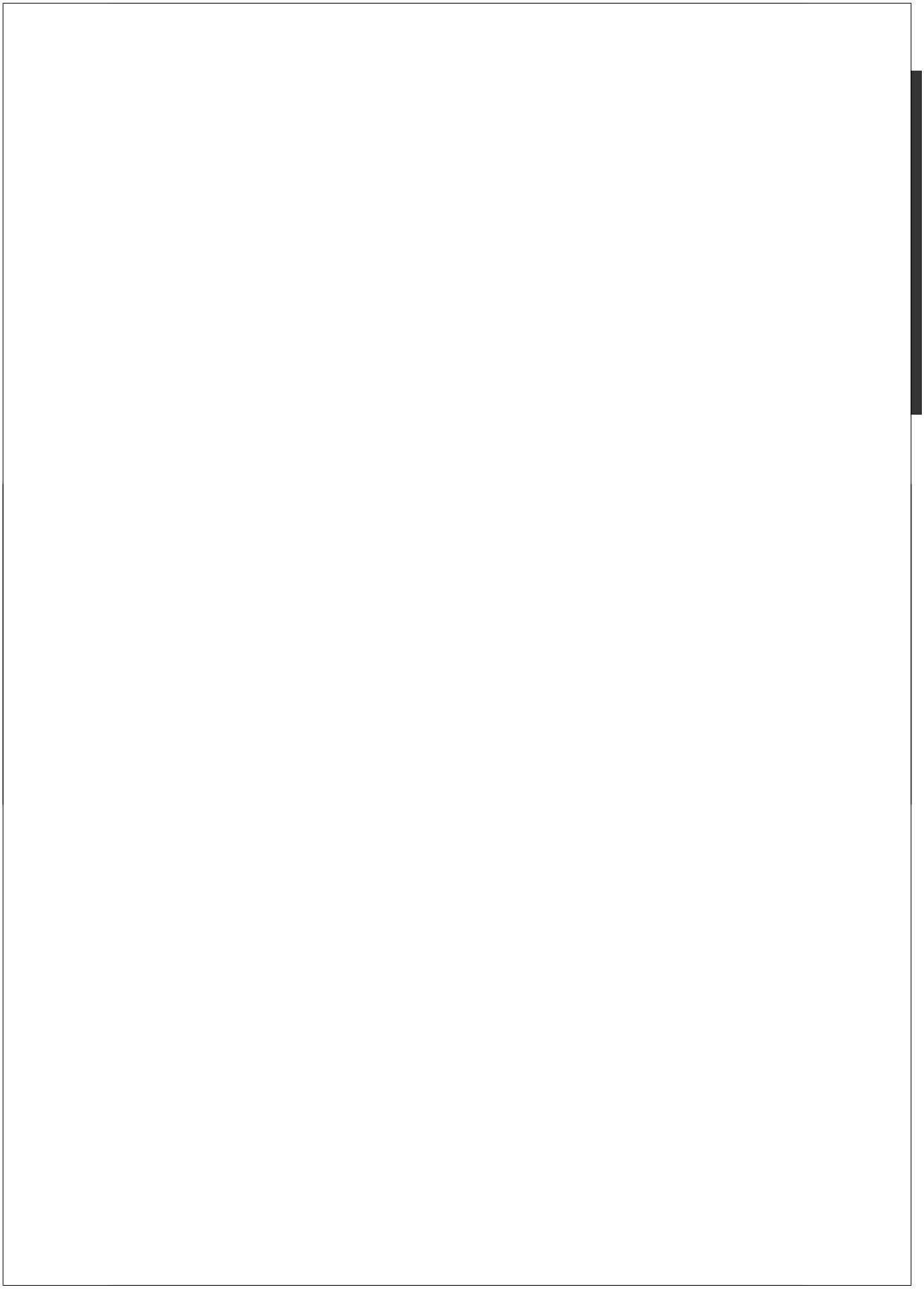
Part II of this thesis focuses on young adults, aged 18 to 30 years. **Chapter 4** addresses which characteristics and environmental factors of cannabis users influence the association with poor mental health, including age of first cannabis use and gender. **Chapter 5** describes how the association between cannabis use and specific profiles of subclinical symptoms in young adulthood is influenced by both intensity and age onset of use. Like chapter 2, **Chapter 6** aims at elucidating the nature of the relationship between cannabis use and mental health. Particularly, it addresses the role of cigarette smoking, by comparing the crude association of cannabis use with psychotic-like experiences to a model that adjusts for cigarette smoking.

Chapter 7 provides a summary of the results, methodological considerations and implications for further research, leading up to a general conclusion and implications.



Part I

Adolescence



2 Cannabis use as an indicator of risk for mental health problems in adolescents

a population-based study at secondary schools

W. A. van Gastel[1]

W. Tempelaar[1]

C. Bun[2]

C. D. Schubart[1]

R. S. Kahn[1]

C. Plevier[2]

M. P. M. Boks[1]

Psychological Medicine (2012) **3**, 1-8.

1. Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Department of Psychiatry, HP. B01.206, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands

2. Public Health Service Greater Utrecht area (GGD Midden Nederland), De Dreef 5, 3706 BR Zeist, the Netherlands

ABSTRACT

Background

Although the association between cannabis use and a wide range of psychiatric symptoms is fairly well established, it is not clear whether cannabis use is also a risk factor for general mental health problems at secondary school.

Methods

10,324 secondary school children aged 11-16 years, participating in an ongoing Public Health Service School Survey, gave information on demographics, substance use, school factors, stressful life-events and filled out the Strengths and Difficulties Questionnaire (SDQ).

Results

Cannabis use in the past month was associated with a clinically relevant score on the SDQ (unadjusted OR 4.46, 95% CI 3.46-5.76). Other risk factors associated with poor psychosocial functioning were: a low level of education, alcohol use, cigarette smoking, hard drug use, frequent truancy, an unfavourable school evaluation, feeling unsafe at school, being victimized, frequent absence due to illness, a mentally ill parent, molestation by a parent, financial problems and feeling distressed by an adverse event. In a full model adjusting for these risk factors, cannabis was not significantly associated with mental health problems, although an association at trend-level was apparent.

Of these risk factors, regular alcohol use, cigarette smoking, hard drug use, frequent truancy, an unfavourable school evaluation and frequent absence due to illness were also associated with cannabis use.

Conclusions

The association between cannabis use and poor psychosocial functioning in adolescence is, at least in part, due to confounding by other risk factors. Thus, cannabis use can best be viewed as an indicator of risk for mental health problems in adolescence.

INTRODUCTION

Adolescent cannabis use, regular or heavy use in particular, has been implicated as a risk factor for a range of psychiatric symptoms. Increased rates of externalizing as well as internalizing problems have been reported by young cannabis users, such as delinquent behaviour, conduct disorder and attention problems (Fergusson *et al.* 2002), psychotic symptoms (Arseneault *et al.* 2002), anxiety and depressive symptoms (Degenhardt *et al.* 2003). In particular those who started to use cannabis before the age of 16 years report an elevated rate of symptoms: psychotic symptoms (Arseneault *et al.* 2002; Arseneault *et al.* 2002; McGrath *et al.* 2010; McGrath *et al.* 2010; Schubart *et al.* 2010), adjustment problems including depression, crime and suicidal behaviour (Fergusson *et al.* 2002), anxiety (Hayatbakhsh *et al.* 2007), externalizing behaviour (Hayatbakhsh *et al.* 2008) and in the cognitive domain attentional dysfunction (Ehrenreich *et al.* 1999), poor educational achievement (Horwood *et al.* 2010) and poor executive functioning (Fontes *et al.* 2011). The risk increases with higher frequency and longer duration of use for psychosis (Arseneault *et al.* 2002; Monshouwer *et al.* 2006, Schubart *et al.* 2010; van Gastel *et al.* 2012), depression and anxiety (Fergusson *et al.* 2002; Patton *et al.* 2002; Degenhardt *et al.* 2003; Hayatbakhsh *et al.* 2008) and adjustment problems (Fergusson *et al.* 2002). Especially the combination of heavy use and young age at onset is associated with a high risk for psychiatric disorders (Schubart *et al.* 2010; Rubino *et al.* 2011).

Although cannabis use has been related to a diverse range of psychiatric symptoms, it is less clear what relationship it bears with general psychosocial function. Focusing on psychosocial functioning allows for comprehensive screening and facilitates early detection of symptoms. In a previous study, Hollis and colleagues (Hollis *et al.* 2008) investigated the relationship between cannabis use and a composite measure of psychosocial functioning. They found an association between cannabis use and mental health problems, but it was limited to adolescents at genetic high risk for schizophrenia: such an association was not found in adolescents with ADHD and healthy controls. Since the focus of public mental health strategies lies in the general population, knowing the relationship between cannabis use and poor psychosocial functioning in the general population is important. In this study, we set out to investigate whether cannabis use in secondary school children is associated with poor psychosocial functioning, in isolation and in combination with an extensive set of other risk factors. Secondly, in order to elaborate on this, we investigate the association between cannabis use itself and other known determinants of psychosocial functioning.

METHODS

Participants

The current sample was obtained in the 2007 wave of a regular survey at secondary schools by the Dutch Public Health Service of the greater Utrecht area (GGD Midden-Nederland). The survey took place at 71% of all secondary schools in the region, except in the inner-city (the city of Utrecht). Reasons for schools not participating were: a full agenda, recent change in management or other ongoing research. Of all students on the participating schools, 84% filled out the questionnaire. All students were asked to complete the digital questionnaire anonymously in the classroom. Data were collected on psychosocial functioning, lifestyle and social environment including perceived school safety using a computer based assessment in class. A designated member of staff ensured good research related communication with parents and students. Students were provided contact information of the Public Health Service. Furthermore, during the questionnaire students could fill in their name and contact information in case they felt like talking to someone following the survey. A nurse of the Community Health Service contacted these adolescents. Schools in both rural and urban areas were included; about 34% of the study population lives in an urban area. Of the total sample, participants outside the age range of 11-16 were excluded, resulting in a sample of 10,324 adolescents.

Measurements

Psychosocial functioning

Psychosocial functioning was measured by self-report, using the Strengths and Difficulties Questionnaire (SDQ, (Goodman *et al.* 1998). The SDQ has been developed for adolescents aged 11 to 16 years and was found to correctly predict psychiatric diagnoses in 81-91% of the cases (Goodman *et al*. 2000). The SDQ measures psychosocial adjustment of children and adolescents and assesses the most important domains of child psychopathology, being emotional problems, conduct problems, hyperactivity and peer problems. Apart from weaknesses, the SDQ also measures strengths, in the form of pro-social behaviour.

The Dutch translation of the self-reported SDQ has been validated (Muris *et al.* 2003; Widenfelt *et al.* 2003). The internal consistency of the total difficulties score was found to be reasonable. The SDQ consists of 25 items on psychological attributes, scoring on a 3-point Likert scale (not true/somewhat true/certainly true). The SDQ total difficulties score can be divided into a normal (0 to 15), borderline (16 to 19) and clinical score (20 to 40) (Goodman *et al.* 1998). In order to identify those with clinically relevant symptoms, the outcome was dichotomised into normal to borderline (-1) and clinical (1).

To further explore the results, the association of cannabis use with the subscales of emotional problems, hyperactivity problems and pro-social behaviour were assessed;

these subscales were found to have reasonable internal consistency, as opposed to the conduct and peer relationship problems scale, which were found to have an internal consistency below acceptable limits (Muris *et al.* 2003; Widenfelt *et al.* 2003). These scores were recoded into normal to borderline (-1) and clinical (1).

Use of cannabis and other substances

Cannabis use was assessed by asking 'How many times did you use cannabis during the past four weeks?' (never/monthly/at least weekly/more than five times weekly). The answers were recoded into -1 (no use during the past month) and 1 (used once or more). Smoking cigarettes (classified the same as cannabis use) was recoded to current smoking; of the smokers 60.6% smoked at least weekly. Alcohol use (never/monthly/at least weekly/daily) was recoded to at least once a month. Use of hard drugs was coded as ever use of any illicit drug other than tobacco, alcohol or cannabis.

Socio-demographic factors

Several socio-demographic measures were included: age (in years), gender, ethnicity (Dutch, Dutch Antillean, Turkish, Moroccan or other non-native: dichotomised into native or non-native, when one or more parents were born abroad), level of education (preparatory vocational versus preparatory polytechnic/scientific) and household composition (living with both biological parents versus one or none of them). A mentally ill parent was included as a (crude) proxy for genetic predisposition for mental health complaints (Mattejat and Remschmidt, 2008).

School variables

Truancy was coded into never or rarely versus more than three hours during the past 4 weeks. The student's evaluation of school was measured by the question 'How do you like school?' and recoded into 'not at all/not much' versus 'quite/a lot'. Feeling safe in school was measured by 'Do you ever feel unsafe in school', with answers dichotomised into never versus sometimes/often. School victimization was coded ever/never. Absence due to illness was considered regular when a subject missed out on more than five schooldays during the past 4 weeks.

Stressful life-events

Subjects were inquired after lifetime experience of the following: a deceased beloved one, separation of parents, domestic violence (between parents or victimizing the adolescent), molestation by someone other than a parent, sexual abuse, financial problems (of parents or of the adolescent) or any other stressful event. Items were considered a risk factor when they were endorsed to be a nuisance.

Data analysis

All analyses were carried out with the statistical package for the social sciences (SPSS 20.0) . There were 116 missing values for level of education, one for perceived school unsafety and one for victimization; listwise exclusion was applied. First, difference in characteristics between those with a normal or borderline SDQ-score (0-20) and those with a clinically relevant score (>20) was assessed by two-sided Chi-square tests. Second, multicollinearity was investigated by means of bivariate non-parametric correlations (Kendall's $\tau < 0.8$; Stevens, 2002). Third, logistic regression analyses (yielding odds ratios (OR) with 95% confidence intervals) were carried out, with clinical SDQ-score as dependent variable. This was done univariately, with only cannabis use as a predictor, and repeated in a full model including potential confounders. These were included if significant at $p<0.05$ or if they changed the predictive value (OR) of cannabis use by 10% or more (Greenland, 1989; Chaves *et al.* 2007). In addition, interactions of cannabis use with confounders were determined. Post-hoc analyses were performed to specify the association with substance use, by means of dummy variables of smoking, alcohol and cannabis use (never/less than weekly/at least weekly/more than five times weekly or daily). Also, post-hoc analyses were performed on the subscales of emotional problems, hyperactivity and pro-social behaviour.

Finally, a logistic regression analysis with cannabis use as an outcome measure and clinical SDQ-score as a predictor was performed, selecting predictors based on univariate regressions (threshold of $p<0.05$ or a change in OR of at least 10%) and combining them into a full model. Post-hoc analyses were performed for frequency of smoking and alcohol use and for ethnicity.

RESULTS

The sample consisted of 5179 girls (50.2%) and 5145 boys (49.8%). The average age was 13.9 years (sd 1.3 years). The characteristics of the sample are presented in table 1 (and Table S1 in the supplement, excluding users of hard drugs), split for those with a normal/borderline SDQ total score, versus those with a clinically relevant score. Gender, age and ethnicity did not differ significantly between groups, in contrast to all of the other risk factors. Of subjects with a normal or borderline SDQ total score, 4.7% used cannabis during the past month, as opposed to 18.1% in the group with a clinical SDQ-score.

Multicollinearity was improbable, since Kendall's τ was below 0.8 for all intercorrelations. Based on univariate analyses, gender, age and ethnicity were not associated with a clinical SDQ-score. Cannabis use was not associated with perceived school unsafety and being victimized univariately.

Table 1. Characteristics (n, % of total) of the full sample and split for clinically relevant SDQ-score (normal or borderline score: 0-19, clinically relevant score: 20-40)

	Full sample ***(n=10.324)***	**Normal SDQ-** ***score (n=9.864)***	**Clinical SDQ-** ***score (n=460)***
Female gender	5179 (50.2%)	4963 (50.3%)	216 (47.0%)
Ethnicity ‡			
Dutch	8403 (81.4%)	8030 (81.4%)	373 (81.1%)
Surinam, Antillean, Aruban	283 (2.7%)	274 (2.8%)	9 (2.0%)
Turkish	269 (2.6%)	252 (2.6%)	17 (3.7%)
Moroccan	374 (3.6%)	362 (3.7%)	12 (2.6%)
Other	995 (9.6%)	946 (9.6%)	49 (10.7%)
Low education level *	5652 (54.7%)†	5327 (54.0%)†	325 (70.7%)†
Lives separate from one or both parents *	2235 (21.6%)	2094 (21.2%)	141 (30.7%)
Mentally ill parent *	591 (5.7%)	519 (5.3%)	72 (15.7%)
Regular truant *	571 (5.5%)	479 (4.9%)	92 (20.0%)
Unfavourable school evaluation *	4306 (41.7%)	3977 (40.3%)	392 (71.5%)
Perceived school unsafety *	2424 (23.5%)†	2164 (21.9%)†	260 (56.5%)†
Ever been bullied *	1953 (18.7%)†	1741 (17.7%)†	212 (46.1%)†
Frequent absence due to illness *	455 (4.4%)	402 (34.1%)	53 (11.5%)
Smokes cigarettes *	1554 (15.1%)	1383 (14.0%)	171 (37.2%)
Consumed alcohol last month *	3958 (38.3%)	3687 (37.4%)	271 (58.9%)
Frequency of cannabis use*‡			
Never	9,777 (94.6%)	9,400 (95.3%)	377 (81.9%)
< weekly	328 (3.2%)	287 (2.9%)	41 (8.9%)
> weekly	162 (1.6%)	135 (1.4%)	27 (5.9%)
> Five times a week	57 (0.6%)	42 (0.4%)	15 (3.3%)
Illicit drug use ever*	217 (2.1%)	167 (1.7%)	50 (10.9%)
Stressful life-event			
*a deceased loved one**	882 (8.5%)	800 (8.1%)	82 (17.8%)
*separation of parents **	455 (4.3%)	407 (4.1%)	38 (8.3%)
*domestic violence parents**	61 (0.6%)	49 (0.5%)	12 (2.6%)
*molestation by parent**	91 (0.9%)	68 (0.7%)	23 (5.0%)
*molestation by other**	26 (0.3%)	19 (0.2%)	7 (1.5%)
*sexual abuse**	85 (0.8%)	66 (0.7%)	19 (4.1%)
*own financial problems**	186 (1.8%)	147 (1.5%)	39 (8.5%)
*financial problems parent(s) **	255 (2.5%)	216 (2.2%)	39 (8.5%)
*any other stressful event**	629 (6.1%)	552 (5.6%)	77 (16.7%)

**significant difference between the two groups at p>0.001, applying a two-sided Chi-square test*
† missing values: 116 for level of education, 1 for perceived school unsafety and 1 for ever been bullied
‡ for comparison, two groups were created, with native versus non-native for ethnicity and with at least monthly use as cut-off for cannabis use

Risk factors for poor psychosocial functioning

The odds ratios for a clinical SDQ-score are shown in table 2 (and Table S2 excluding hard-drug users). The unadjusted OR for a clinical SDQ score in cannabis users (versus never users) was 4.46 (95% CI: 3.46-5.76, p<0.001). After adjusting for the full set of risk factors, the OR was reduced to 1.41 (95% CI: 0.99-2.01) and was not significant anymore (p=0.058). Other significant predictors of SDQ were smoking, alcohol use, hard drug use, a low education level, frequent truancy, an unfavourable school evaluation by the student, perceived school unsafety, having been bullied, frequent absence due to illness, a mentally ill parent, molestation by a parent, financial problems and any other stressful event. Cannabis use in the past month interacted significantly with hard drug use and with a mentally ill parent (both at p<0.05), indicating that adolescents who use both cannabis and hard drugs and those who have a mentally ill parent and use cannabis are at increased risk for a clinical SDQ-score. The full model explained 21.8% of a clinical SDQ total score (Nagelkerke R^2). Post-hoc regression analyses applying dummy variables of substance use showed no significant differences of frequency of cigarette smoking and cannabis use, although we had limited power to detect such differences. For alcohol use, a dose-response effect was apparent, with an OR ranging from 1.34 for monthly use (95% CI: 1.03-1.72, p<0.05) to 3.26 for alcohol use of more than five times a week (95% CI:1.84-5.87, p<0.001). Post-hoc analyses on the SDQ subscales of emotional problems, hyperactivity and prosocial functioning revealed no significant predictive value of cannabis use.

Table 2. Association between cannabis use in the past month and a clinical SDQ-score; Odds Ratios (95 % Confidence Interval)

Model	Predictor	Odds Ratio (95 % CI)
Unadjusted	**Cannabis use**	4.46 (3.46-5.76)**
Fully adjusted	**Cannabis use**	1.41 (0.99-2.01)♦
	Low education level	1.21 (1.08-1.35)*
	Mentally ill parent	2.02 (1.49-2.76)**
	Regular truant	2.52 (1.87-3.40)**
	Unfavourable school evaluation	2.44 (1.96-3.04)**
	Perceived school unsafety	2.78 (2.23-3.46)**
	Ever been bullied	2.36 (1.89-2.95)**
	Frequent absence due to illness	1.50 (1.04-2.16)*
	Smokes cigarettes	1.62 (1.24-2.11)**
	Alcohol use	1.40 (1.11-1.76)*
	Hard drug use ever	1.61 (1.03-2.50)*
	Stressful life-event	
	a deceased loved one	ns
	separation of parents	ns
	domestic violence parents	ns
	molestation by parent	2.04 (1.09-3.83)*
	molestation by other	ns
	sexual abuse	ns
	own financial problems	2.16 (1.39-3.35)*
	financial problems parent(s)	ns
	any other stressful event	1.53 (1.12-2.08)*

ns: non-significant

♦ non-significant, but with trend (p=0.058)

** significant at p<0.05*

*** significant at p<0.001*

Risk factors for cannabis use

The odds ratios for cannabis use are shown in table 3 (S3). Participants who smoked cigarettes had the highest odds ratio for cannabis use in the past month: 8.93 (95% CI: 7.03-11.36, p<0.000). Alcohol use, cigarette smoking, hard drug use, frequent truancy, an unfavourable school evaluation by the student and frequent school absence due to illness were also associated with cannabis use (as well as to a clinical SDQ-score). Furthermore, male gender, being older, non-native ethnicity, and living separated from one or both parents were independent risk factors for cannabis use in the past month. A clinical SDQ score predicted cannabis use at a borderline significant level (p=0.051). In total, 46.3% of cannabis use was explained by these risk factors (Nagelkerke R^2). Post-hoc regression analyses of the quantity of substance use showed a dose-response effect for smoking as well as for alcohol consumption on cannabis use. Corrected odds ratios for using cannabis increased from 4.86 (95% CI: 3.26-7.24) for monthly alcohol consumption to 18.02 (95% CI: 10.27-31.62, all significant at p<0.000) for consumption more than five times a week (reference group: no alcohol use in the past month). Corrected odd ratios for cannabis use increased with frequency of smoking in a similar fashion: from 3.57 (95% CI: 2.47-5.17) for monthly, to 9.21 (95% CI: 7.02-12.08) for daily smoking (all significant at p<0.000; reference group no smoking during the past month). Post-hoc analyses for ethnicity showed that adolescents with one or more parents born in the Netherlands Antilles had an OR of 1.81 (95% CI: 1.01-3.26, p<0.05) for cannabis use in the past month. Adolescents with parents from a non-native ethnicity other than Dutch Antillean, Turkish or Moroccan had an OR of 1.95 (95% CI: 1.42-2.68, p<0.001) for cannabis use in the past month.

Table 3. Risk factors for cannabis use in the past month; Odds Ratios (95 % Confidence Interval)

Model	Predictor	Odds Ratio (95 % CI)
	Male gender	2.13 (1.70-2.67)**
	Age	1.39 (1.26-1.54)**
	Ethnicity	1.73 (1.32-2.27)**
	Low education level	ns
	Lives separate from one or both parents	1.17 (1.03-1.32)*
	Mentally ill parent	n.s.
	Regular truant	2.06 (1.56-2.72)**
	Unfavourable school evaluation	1.36 (1.09-1.70)*
	Frequent absence due to illness	1.87 (1.29-2.71)*
	Smokes cigarettes	8.93 (7.03-11.36)**
	Alcohol use	6.24 (4.29-9.08)**
	Hard drug use ever	7.76 (5.40-11.17)**
	Stressful life-event	
	a deceased loved one	ns
	separation of parents	ns
	sexual abuse	ns
	own financial problems	ns
	financial problems parent(s)	ns
	any other stressful event	ns
	Clinical SDQ-score	1.42 (1.00-2.02)♦

ns: non-significant

♦ borderline significant (p=0.051)

** significant at p<0.05*

*** significant at p<0.001*

DISCUSSION

In this large population-based study in secondary school adolescents, we investigated the relationship between cannabis use and psychosocial functioning. Cannabis use in the past month was significantly associated with poor psychosocial functioning univariately, but significance dropped to trend-level after adjusting for confounding by other risk factors. Secondly, we found that six risk factors were associated with an increased risk of poor psychosocial functioning as well as that of cannabis use before the age of 16.

This study adds to our knowledge of the association between cannabis use and mental health in adolescence: it shows that cannabis use is associated with a broad measure of psychosocial functioning in a general population sample. Earlier studies were directed to specific symptom dimensions (e.g. Hayatbakhsh *et al.* 2007; Galera *et al.* 2010; Schubart *et al.* 2010; van Gastel *et al.* 2012) or found that the association was limited to adolescents at high genetic risk for schizophrenia (Hollis *et al.* 2008).

Our results indicate that the relationship with poor psychosocial functioning is at least partly due to confounding, by factors such as use of other substances, truancy and frequent school absence due to illness and argue against a direct causal relationship between cannabis use and poor psychosocial functioning. Also, we found no evidence of a dose-response relationship, which would support a causative effect of cannabis use on poor psychosocial functioning. Our data are consistent with the reverse, whereby poor psychosocial functioning leads to cannabis use, considering that a clinical SDQ-score was predictive of cannabis use in a fully adjusted model. However, this association was only borderline significant and residual confounding is likely to play a role. Thus, our results suggest that the relationship between moderate cannabis use and psychosocial functioning in adolescence is best explained by confounding as was previously proposed by MacLeod et al (2004).

Regardless of the nature of the association, cannabis use can be viewed as a marker for adolescents at risk for mental health problems. If the relationship is indeed due to confounding, intervention strategies aimed at diminishing cannabis use would be to little avail. Public mental health strategies could instead implement these findings by including cannabis use as an indicator of risk. It could serve in a screening profile for adolescents at risk for mental health problems. Especially the interaction effects between cannabis use and both hard drug use and a mentally ill parent could be valuable for this purpose. Future research should aim at defining such a risk profile, whilst assessing the sensitivity and specificity of the profile as a whole. Other factors that might serve this purpose, are the risk indicators that we associated with both poor psychosocial functioning and cannabis use: cigarette smoking, alcohol consumption, frequent truancy, frequent school absence

due to illness and an unfavourable school evaluation by the student. Characteristics that have been previously linked to both cannabis use and psychosocial functioning, but that were not included in the present study, may also be useful. These include low self-esteem, negative mood, peer group substance use, a positive attitude towards substance use and delinquency (von Sydow *et al*. 2002; Husler *et al*. 2005). It is stressed that as opposed to general psychosocial functioning, the relation between cannabis use and specific symptom-dimensions might well be due to more than confounding: longitudinal studies point into the direction of a causal relation with psychotic symptoms in particular (Arseneault *et al.* 2002; Zammit *et al.* 2002; Henquet *et al.* 2005; Moore *et al.* 2007; Kuepper *et al.* 2011).

The most important limitation of this study is its cross-sectional nature. However, results are in line with longitudinal studies defining risk factors for mental health problems (Hollis *et al.* 2008; Emerson *et al.* 2010) as well as for predictors of cannabis use (Korhonen *et al.* 2010). The data were gathered by self-report, possibly leading to either over- or underreporting of undesirable or sensitive information, such as on cannabis use, financial problems and stressful life-events. However, by administering the questionnaires in school classes and by assuring anonymity, validity and reliability are assumed to improve (Smit *et al.* 2002). Regarding cannabis use, studies comparing psychometric and biometric measures (among which urine and hair-tests) show good reliability of self-report measures (Ledgerwood *et al.* 2008; Zaldivar *et al.* 2009). Still, the applied measure of cannabis use was rather crude and age at onset of use was not assessed. However, given the age range of our sample, all cannabis users in our study had a young age at first use. The small age range does not allow for effective statistical analysis. At class-level, a selection bias could have occurred, missing out truants and those who often miss school due to illness. Since truancy is positively associated to substance use and mental health problems, this bias is more likely to have led to an underestimation of the effect. Finally, specific information on social-economic status and urbanicity was not collected.

Despite its limitations, we think that the present study is important, since it demonstrates the relevance of cannabis use as a risk factor for poor psychosocial functioning in secondary school children. Although we show that confounding partly, if not entirely, explains this relationship, cannabis use is associated with many known risk factors and therefore can be viewed as an indicator of risk for mental health problems at this vulnerable age.

ACKNOWLEDGEMENTS

We are grateful to the participating schools and the Public Health Service of the Greater Utrecht area (GGD Midden Nederland) for facilitating data-collection.

SUPPLEMENTARY FILES*:* ANALYSES WITHOUT HARD DRUG USERS

Table S1. Characteristics (n, %) of the full sample and split for clinically relevant SDQ-score (normal or borderline score: 0-19, clinically relevant score: 20-40)

	Full sample ***(n=10.107)***	**Normal SDQ-** ***score (n=9.697)***	**Clinical SDQ-** ***score (n=410)***
Female gender	5073 (50.2%)	4878 (50.3%)	195 (47.6%)
Ethnicity ‡			
Dutch	8235 (81.5%)	7898 (81.4%)	337 (82.2%)
Surinam, Antillean, Aruban	279 (2.8%)	271 (2.8%)	8 (2.0%)
Turkish	262 (2.6%)	248 (2.6%)	14 (3.4%)
Moroccan	368 (3.6%)	358 (3.7%)	10 (2.4%)
Other	963 (9.5%)	922 (9.5%)	41 (10.0%)
Low education level **	4492 (54.3%)†	5204 (53.7%)†	288 (70.2%)†
Lives separate from one or both parents **	2153 (21.3%)	2033 (21.0%)	120 (29.3%)
Mentally ill parent **	558 (5.5%)	499 (5.1%)	59 (14.4%)
Regular truant **	501 (5.0%)	433 (4.5%)	68 (16.6%)
Unfavourable school evaluation **	4163 (41.2%)	3874 (40.0%)	289 (70.5%)
Perceived school unsafety **	2348 (23.2%)†	2116 (21.8%)†	232 (56.6%)†
Ever been bullied **	1885 (18.7%)	1699 (17.5%)	186 (45.4%)
Frequent absence due to illness **	414 (4.1%)	379 (3.9%)	35 (8.5%)
Smokes cigarettes **	1400 (13.9%)	1259 (13.0%)	141 (34.4%)
Consumed alcohol last month **	3770 (37.7%)	3540 (36.5%)	230 (56.1%)
Frequency of cannabis use **‡	420 (4.2%)	367 (3.8%)	53 (12.9%)
Never	9,687 (95.8%)	9,330 (96.2%)	357 (87.1%)
< weekly	283 (2.8%)	252 (2.6%)	31 (7.6%)
> weekly	111 (1.1%)	92 (0.9%)	19 (4.6%)
> Five times a week	26 (0.3%)	23 (0.2%)	3 (0.7%)

Table S1. Continued.

	Full sample ***(n=10.107)***	**Normal SDQ-** ***score (n=9.697)***	**Clinical SDQ-** ***score (n=410)***
Stressful life-event			
*a deceased loved one***	843 (8.3%)	776 (8.0%)	67 (16.3%)
*separation of parents **	427 (4.2%)	397 (4.1%)	30 (7.3%)
*domestic violence parents***	54 (0.5%)	44 (0.5%)	10 (2.4%)
*molestation by parent***	76 (0.8%)	61 (0.6%)	15 (3.7%)
*molestation by other***	17 (0.2%)	12 (0.1%)	5 (1.2%)
*sexual abuse***	66 (0.7%)	57 (0.6%)	9 (2.2%)
*own financial problems***	167 (1.7%)	136 (1.4%)	31 (7.6%)
*financial problems parent(s) ***	240 (2.4%)	206 (2.1%)	34 (8.3%)
*any other stressful event***	167 (1.7%)	524 (5.4%)	65 (15.9%)

** significant difference between the two groups at p>0.01, applying a two-tailed Mann-Whitney U rank sum test*

** *significant difference between the two groups at p>0.001, applying a two-tailed Mann-Whitney U rank sum test*

† missing values: 111 for level of education, 1 for perceived school unsafety

‡ for comparison, two groups were created, with native versus non-native for ethnicity and with at least monthly use as cut-off for cannabis use

Table S2. Association between cannabis use in the past month and a clinical SDQ-score; Odds Ratios (95 % Confidence Interval)

Model	Predictor	Odds Ratio (95 % CI)
Unadjusted	**Cannabis use**	3.77 (2.78-5.13)**
Fully adjusted	**Cannabis use**	1.59 (1.09-2.32)*
	Low education level	1.20 (1.06-1.34)*
	Lives separate from one or both parents	ns
	Mentally ill parent	2.07 (1.49-2.86)**
	Regular truant	2.68 (1.94-3.68)**
	Unfavourable school evaluation	2.45 (1.95-3.08)**
	Perceived school unsafety	2.89 (2.30-3.64)**
	Ever been bullied	2.36 (1.87-2.98)**
	Frequent absence due to illness	ns
	Smokes cigarettes	1.80 (1.37-2.38)**
	Alcohol use	1.35 (1.01-1.71)*
	Stressful life-event	
	a deceased loved one	ns
	separation of parents	ns
	domestic violence parents	ns
	molestation by parent	ns
	molestation by other	ns
	sexual abuse	ns
	own financial problems	2.07 (1.29-3.32)*
	financial problems parent(s)	ns
	any other stressful event	1.67 (1.20-2.30)*

ns: non-significant
** significant at p<0.05*
*** significant at p<0.001*

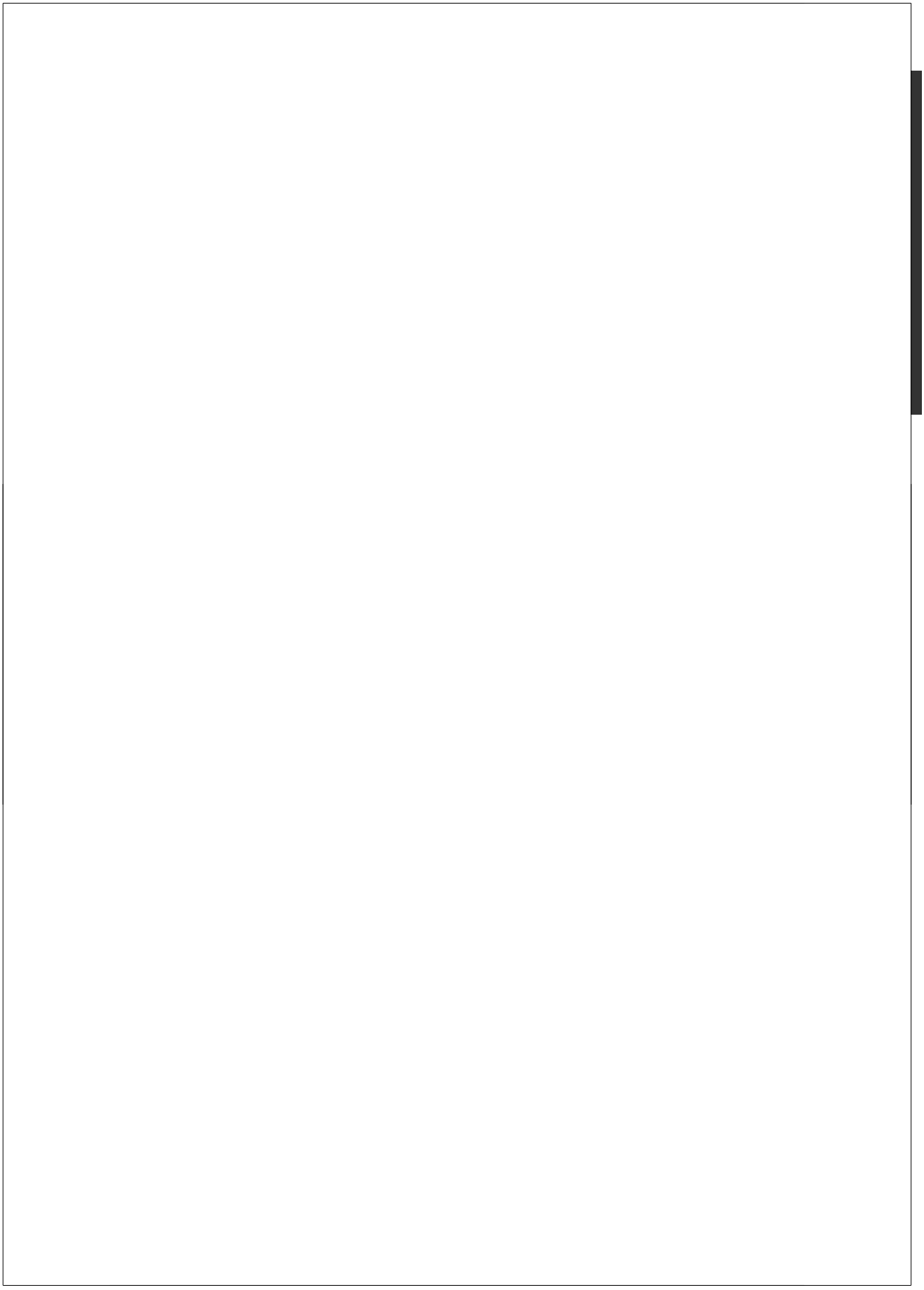
Table S3. Risk factors for cannabis use in the past month; Odds Ratios (95 % Confidence Interval)

Model	Predictor	Odds Ratio (95 % CI)
	Gender	2.17 (1.70-2.76)**
	Age	1.44 (1.29-1.60)**
	Ethnicity	1.76 (1.32-2.35)**
	Low education level	ns
	Lives separate from one or both parents	1.20 (1.05-1.37)*
	Mentally ill parent	ns
	Regular truant	1.90 (1.41-2.56)**
	Unfavourable school evaluation	1.29 (1.03-1.63)*
	ever been bullied	ns
	Frequent absence due to illness	1.72 (1.14-2.59)*
	Smokes cigarettes	9.78 (7.57-12.63)**
	Alcohol use	6.89 (4.54-10.48)**
	Stressful life-event	
	a deceased loved one	ns
	separation of parents	ns
	sexual abuse	ns
	own financial problems	ns
	financial problems parent(s)	ns
	any other stressful event	ns
	Clinical SDQ-score	1.51 (1.03-2.22)*

ns: non-significant

** significant at p<0.05*

*** significant at p<0.001*



3 Cannabis use and subclinical positive psychotic experiences in early adolescence

findings from a Dutch survey

W. A. van Gastel[1]

J. T. W. Wigman[2]

K. Monshouwer[2,3]

R. S. Kahn[1]

J. van Os[4,5]

M. P. M. Boks [1,6]

W. A. M. Vollebergh[2]

Addiction (2012) **107***,* 381-387

1. Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Department of Psychiatry, HP. B01.206, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands

2. Department of Interdisciplinary Social Sciences, University of Utrecht, PO Box 80.140, Heidelberglaan 2, 3508 TC Utrecht, the Netherlands

3. Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Utrecht, PO Box 725. 3500 AS, Utrecht, the Netherlands

4. Department of Psychiatry and Psychology, European Graduate School of Neuroscience, SEARCH, Maastricht University Medical Centre, PO Box 616, 6202 AZ Maastricht, The Netherlands

5. King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK

ABSTRACT

Aims

To investigate the association between early cannabis use and subclinical psychotic experiences, distinguishing between five levels of use: never used, discontinued use (lifetime users who did not use in the preceding year), experimental use, regular use and heavy use.

Design

Cross-sectional observational study.

Setting

Dutch Health Behaviour in School-aged Children (HBSC) study, 2005 wave.

Participants

4552 secondary school children aged 12-16 years.

Measurements

Cannabis Use, CAPE Positive Scale, confounding factors: age, gender, family affluence, household composition, social support, alcohol use, cigarette smoking, ethnicity and urbanicity.

Findings

The association between cannabis use and subclinical positive symptoms was confirmed, and remained significant after extensive adjustment for potential confounders. Associations were found for all user groups, with strongest associations for the discontinued use group (ß=0.061, p = 0.000) and for the heavy use group (ß=0.065, p = 0.000).

Conclusions

This study shows an enduring association between cannabis use at an early age and subclinical positive psychotic experiences, even after abstaining from cannabis for at least one year. These findings warrant special attention for research into enduring effects of cannabis use in early adolescence on mental health in general and (subclinical) psychotic symptoms in particular.

INTRODUCTION

Clinical psychosis can be viewed as the extreme end of a psychosis continuum, ranging from normal functioning, via subclinical psychotic experiences that are mainly transitory, to florid psychosis (Van Os *et al.* 2009). Although mostly discontinuous in nature (Dhossche *et al.* 2002; Hanssen *et al.* 2005; Wiles *et al.* 2006; Dominguez *et al.* 2011), subclinical psychotic experiences can persist and are predictive of clinical psychosis (Poulton *et al.* 2000; Kelleher and Cannon, 2011) when combined with additional external risk factors impacting on development (Cougnard *et al.* 2007; Kuepper *et al.* 2011). Risk factors such as urbanicity (Krabbendam and van Os, 2005; Van Os *et al.* 2002), ethnic minority state or social defeat (Cantor-Graae and Selten, 2005), childhood trauma (Read *et al.* 2005) and cannabis use (Van Os *et al.* 2002; Moore *et al.* 2007; Kuepper *et al.* 2011; Large *et al.* 2011) are associated to clinical psychosis and subclinical psychotic experiences (Van Os *et al.* 2008). These factors seem to have a particularly adverse effect during the specific timeframe of early adolescence (Van Os *et al.* 2008; Schubart *et al.* 2010), a critical period of many biological, psychological and sociological changes (Steinberg, 1999). Cannabis use is one of the few risk factors that may be more liable to prevention, as compared to factors such as for example ethnicity. Studying it more closely could provide health workers with new approaches for intervention.

Cannabis use has been associated with psychotic disorders (Henquet *et al.* 2005; Moore *et al.* 2007) as well as with subclinical psychotic experiences (Monshouwer *et al.* 2006; Schubart *et al.* 2010). The risk of psychosis increases with frequency and duration of use (Zammit *et al.* 2002; Henquet *et al.* 2005; Kuepper *et al.* 2011; McGrath *et al.* 2010). Furthermore, this risk has also been suggested to increase when cannabis is used at an early age, before 15 years; based on cohort studies (Arseneault *et al.* 2002; McGrath *et al.* 2010) and neurobiological findings (Bossong and Niesink, 2010). In line with this, Schubart and colleagues (Schubart *et al.* 2010) found a dose-response relationship of an increase in reported positive psychotic symptoms with younger age of onset.

Since the effect of cannabis on mental health is difficult to address experimentally due to ethical restrictions, observational studies have tried to disentangle the effects of different risk-factors. One of these studies has been done by Monshouwer and colleagues (Monshouwer *et al.* 2006), who showed an association of cannabis use and mental health problems in a sample of 5551 adolescents aged 12-16 years, drawn from the Dutch Health Behaviour in School-aged Children school survey in the 2001 wave. They investigated the association of cannabis and scores on the Youth Self Report, a general instrument to measure mental health problems in adolescents, including Thought Problems, which are strongly associated with subclinical psychotic experiences (Welham *et al.* 2009; Wigman *et al.* 2009). They assessed this association by including an elaborate set of

confounders; first comprising only age and gender and subsequently including other factors such as family affluence, household composition, social support, use of alcohol use and regular smoking. Whereas a dose-response effect was found for more general measures of psychopathology, an effect for Thought Problems was found for heavy users only. Considering that epidemiological studies (Chapman *et al.* 1994; Welham *et al.* 2009) demonstrated that it is specifically the positive symptom dimension that predicts later clinical psychotic outcome, and evidence was found for a dose-response relationship between age of onset and positive psychotic experiences in particular (Schubart *et al.* 2010), more in-depth investigation into this association is warranted.

The present study aims to investigate the association between patterns of cannabis use and positive psychotic experiences. We replicate and refine the study of Monshouwer and colleagues (Monshouwer *et al.* 2006) in the 2005 wave of the Dutch Health Behaviour in School-aged Children school survey, by using the Community Assessment of Psychic Experiences (CAPE), designed to capture subclinical psychotic experiences in the general population while correcting for an elaborate set of potential confounders.

We expect an association between cannabis use and positive psychotic experiences that persists after adjusting for an elaborate set of confounders.

METHOD

Participants

This study was conducted as part of the Dutch 'Health Behaviour in School-aged Children' (HBSC) study, studying health behaviour, health and its social context in youth in Europe and North America (Currie *et al.* 2001). The current data are drawn from the 2005 wave. Participants were selected by a two-stage random sampling procedure: first at school level (proportionate to the number in the corresponding urbanization level; excluding schools for special education) and second by random selection at school class level of one class from every grade (1-4). Response rate at school level was 47% and at class level 93%. Non-response at school level had to do mainly with other research planned or going on (64%). Non-response in classes was low: on average 7% of the students were not reached, mainly because of illness. Schools that did not participate did not differ from participating schools, resulting in a representative sample of Dutch adolescents. Data were collected in October and November 2005. Questionnaires were distributed in classes and administered by trained research assistants during a lesson. Anonymity of the respondents was emphasized when introducing the questionnaires and ensured by collecting all questionnaires in one envelope and sealing the envelope in the presence of the respondents. For the present study, a selection was made of secondary school students aged 12-16.

Instruments

Subclinical positive psychotic experiences

The Community Assessment of Psychic Experiences (CAPE) positive experiences subscale (20 self-reported items) was used to assess lifetime psychotic experiences (Stefanis *et al.* 2002; Konings *et al.* 2006). The CAPE is based on the Peters et al. Delusions Inventory (PDI) (Peters *et al.* 1999), modified to also include hallucinatory experiences. Each item in the CAPE rates two aspects of psychotic experiences: i) frequency and ii) associated distress, both rated on a four-point scale of never/not distressed (1); sometimes/a bit distressed (2); often/quite distressed (3); nearly always/very distressed (4). The frequency and distress items together showed good internal consistency (Cronbach's alpha = 0.94). The sumscore of the 20 frequency items of the positive experiences subscale (CAPE Positive Total) was used as a continuous outcome measure.

Cannabis use

Cannabis use was assessed by asking 'How many times did you use cannabis?' This question was asked for two time frames: lifetime and past-year. Students could answer by ticking the number of times they had used cannabis (never, 1 or 2, 3–5, 6–9, 10–19, 20–39, 40 or more). According to the HBSC standard and following Monshouwer and colleagues (Monshouwer *et al.* 2006) , the results on both answers were combined and recoded into five cannabis use subgroups with cannabis use reported:

1. never;
2. ever, but not during the past year (discontinued use);
3. once or twice during the past year (experimental use);
4. between 3 and 39 times during the past year (regular use);
5. 40 times or more during the last year (heavy use).

First, this five –category measure was recoded into a dichotomous measure of lifetime cannabis use (never versus ever). Second, the five-category variable was used for a more in-depth analysis.

Confounding factors

A number of potential confounding factors were included. The selection of these confounders was based on the outcomes of the 2001 version of the same survey (Monshouwer *et al.* 2006) and of other studies (McGee *et al.* 2000; Rey *et al.* 2002). First, several socio-demographic measures were included: age (in years), gender, household composition (living with both biological parents, one or none of them) and family affluence. The last was assessed using four questions on the presence of material

goods in the family: the student having a bedroom of his/her own, number of computers in the family, number of cars in the family, and number of family holidays in the past year. Together these items can be interpreted as a proxy for prosperity of the family (Currie *et al.* 1997). In accordance with the HBSC protocol (Child and Adolescent Health Research Unit (CAHRU), 2002) the answers were recoded into low, medium or high affluence. Second, social support from father, mother and friends was assessed by the core questionnaire of HBSC (good, poor or no contact) and added as a sum score of social support (Child and Adolescent Health Research Unit (CAHRU), 2002). Third, frequency of alcohol use, as measured by the question 'How often do you take a drink containing alcohol, such as beer, wine, spirits or mixed drinks?' (never, now and again, every month, every week or every day). Answers were recoded into two categories, combining the first two answers in 'seldom or never' and the last three in 'at least every month'. Fourth, daily smoking was included as a confounding factor. Last, in addition to the four models used by Monshouwer and colleagues (Monshouwer *et al.* 2006a), a fifth model was created, including ethnicity and urbanization. Ethnicity was dichotomized into native Dutch versus non-native; with participants belonging to the second category when either the participant, mother or father was not born in the Netherlands. As a measure for urbanization, a five-level scale based on ZIP-codes as developed by HBSC was applied, with 1 being a highly urbanized area and 5 being a rural area .

Data analysis

All analyses were carried out with STATA version 11 for Windows (2009). To obtain correct 95% confidence intervals and *p*-values of past year prevalence of cannabis use in a weighted and clustered sample, robust standard errors were obtained (Skinner *et al.* 1989). To investigate the association between cannabis use and subclinical positive experiences, two sets of multivariate linear regression analyses were conducted.

First, the effect of cannabis use on subclinical psychotic experiences was investigated with the dichotomised variable ('ever' versus 'never'). CAPE total positive sum score was included as outcome variable. The association between cannabis use and subclinical psychotic experiences was investigated using an unadjusted model and a fully adjusted model, comprising age, gender, family affluence, household compositionsocial support, regular alcohol use and daily smoking, in line with Monshouwer and colleagues (Monshouwer *et al.* 2006). Furthermore, ethnicity and urbanization were included. Also, interaction between cannabis use (never vs. ever) and age (12-16 years, continuous) was assessed in the full factorial model.

Second, to investigate the association between cannabis use and subclinical psychotic experiences more in depth, intensity of cannabis use was used (see Measures section)

to investigate the effects of the amount of cannabis: no use ever versus discontinued, experimental, regular and heavy use. This five-category variable was included in the model as an independent variable using dummies with no use as reference group, while correcting for the full set of confounders. To provide insight into the differences in CAPE-scores between the user groups, post-hoc analyses of variance have been carried out. Correcting for multiple testing was done by means of the Tukey's post-hoc test. Interaction of age with cannabis use was analysed in the full model with CAPE positive score as dependent. Cannabis use was entered as a discrete variable with 4 levels of use and non-use as reference, age was entered as a continuous variable.

RESULTS

The sample consisted of 4552 participants, aged 12-16 years old, all secondary school students and 50% females. Table 1 shows the reported cannabis use ever. Almost 14% had ever used cannabis at the time of the interview; comprising of 2.5% of lifetime users who had not used in the previous year; 4.6% experimental users (once or twice in the past year), 5.7% regular users (3-39 times in the past year) and 1.5% heavy users (>39 times in the past year). Past year cannabis use increased with age (one-way ANOVA, $F(4,4547)= 94.84$, $p= 0.000$). Table 2 shows the mean CAPE positive subscale score.

Association between cannabis use ever and subclinical positive psychotic experiences

The standardized regression estimates (β) for the association between cannabis use ever and positive psychotic experiences, as measured by the CAPE for the unadjusted as well as the fully adjusted model, are shown in Table 3. The results show that cannabis use among adolescents was related to subclinical positive experiences, even when an elaborate set of confounders was taken into account ($\beta=0.088$, $p=0.000$). A significant interaction between cannabis use and age was apparent ($\beta=0.081$, $p=0.000$), indicating that the association between cannabis use and subclinical positive psychotic experiences are strongest for the youngest children (figure 1).

Table 1. Frequency of lifetime cannabis use for different ages and user groups. Cannabis use is depicted for each of the user groups a part, as well as summarized in the 'Ever Use, total subgroups' column.

Age (years)	never		Discontinued use		Experimental use		Regular use		Heavy use		Ever use (Total subgroups)		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
12	719	98	4	0.5	7	1.0	4	0.5	0	0	15	2	734	100
13	994	94.3	17	1.6	26	2.5	14	1.3	3	0.3	60	5.7	1054	100
14	1015	87.5	23	2.0	53	4.6	58	5	11	0.9	145	12.5	1160	100
15	853	76.3	45	4.0	80	7.1	108	9.7	32	2.9	265	23.7	1118	100
16	316	65.0	26	5.3	44	9.1	77	15.8	23	4.8	170	35	486	100
Total	3897	85.6	115	2.5	210	4.6	261	5.8	69	1.5	655	14.4	4552	100

Table 2. CAPE positive subscale score, mean and 95% confidence intervals for different age and user groups

Age (years)	never		Discontinued use		Experimental use		Regular use		Heavy use	
	mean	95%C.I.	mean	95%C.I.	mean	95%C.I.	mean	95%C.I.	mean	95%C.I.
12	26.9	26.4-27.4	38.5	32.1-44-9	29.6	24.8-34.4	34.0	27.6-40.4	-	-
13	26.8	26.4-27.2	30.3	27.2-33.4	27.5	25.0-30.0	36.6	33.2-40.0	25.7	18.3-33.0
14	27.1	26.7-27.5	31.9	29.2-34.5	28.2	26.5-30.0	30.0	28.3-31.7	32.5	28.6-36.3
15	27.2	26.8-27.7	28.9	27.0-30.8	30.6	29.2-32.0	28.9	27.7-30.2	30.9	28.7-33.1
16	27.6	26.9-28.3	31.7	29.2-34.2	27.3	25.4-29.3	28.2	26.7-29.6	28.1	25.5-30.8

Table 3. Association between cannabis use ever and CAPE positive scale for the unadjusted and the fully adjusted model. For the fully adjusted model, associations between all factors and CAPEscore are also displayed. βs with a p-value below 0.05 are printed in italic.

Model	**Predictor**	β (p-value)
Unadjusted model	Cannabis use ever	*0.138 (0.000)*
Fully adjusted model	Cannabis use ever	*0.088 (0.000)*
	Age	-0.007 (0.683)
	Female gender	*0.089 (0.000)*
	Family affluence	-0.030 (0.068)
	Household composition	*-0.056 (0.000)*
	Social support	*-0.152 (0.000)*
	Regular alcohol use	*0.069 (0.000)*
	Daily Smoking	0.022 (0.225)
	Urbanicity	*-0.044 (0.008)*
	Ethnicity	*0.052 (0.003)*

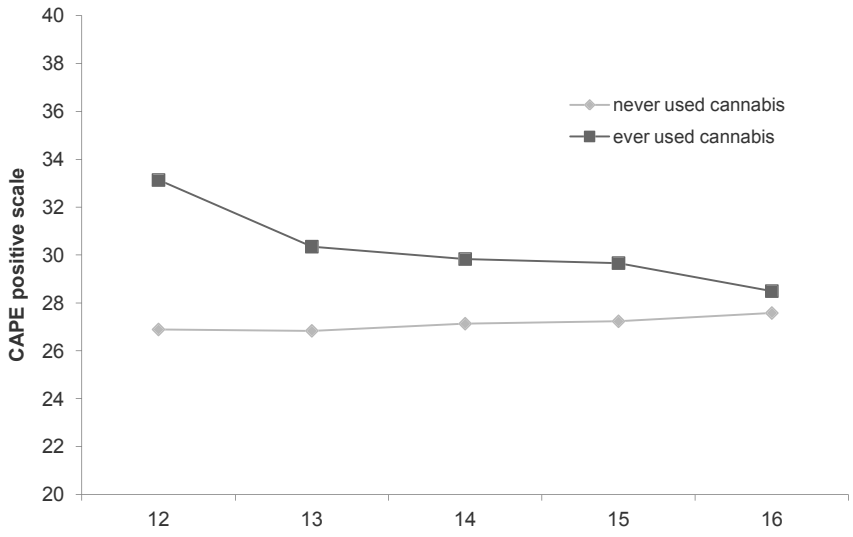


Figure 1. Mean CAPE score for cannabis use ever versus never, for each age category

Association between amount of cannabis use and subclinical positive psychotic experiences
Using the never use group as reference category, the associations of every level of cannabis consumption with the CAPE Positive experiences subscale were significant: Discontinued Use β=0.061 (p=0.000), Experimental Use β=0.037 (p=0.018), Regular Use β=0.048 (p=0.005) and Heavy Use β=0.065 (p=0.000). Additional analyses of variances, corrected for multiple testing by Tukey's post-hoc test, revealed no significant differences in CAPE score between the user groups themselves (e.g. discontinued vs. regular use).

Interaction between age and cannabis use on CAPE positive score was significant for all users groups: Discontinued Use β=-0.080 (p=0.038), Experimental Use β=-0.0337 (p=0.000), Regular Use β=-0.586 (p=0.000) and Heavy Use β=-0.376 (p=0.001).

DISCUSSION

This study investigated the association between cannabis use and subclinical positive psychotic experiences, distinguishing different user groups in a large adolescent general population sample. The results confirm that early cannabis use is associated with subclinical positive psychotic experiences. The strength of this association weakened when correcting for an elaborate set of confounders, but remained significant. Although effect sizes were small, a dose-response association between cannabis use and positive experiences was apparent. Contrary to findings of Monshouwer and colleagues (Monshouwer *et al.* 2006), associations were not only present in those who had used cannabis regularly and recently but were present in all users groups. Most notably, the associations of cannabis use with psychotic experiences were similar in the Discontinued Use and the Heavy Use group.

Frequency of cannabis use
Regarding the three levels of last year use (experimental, regular and heavy use), a dose-response relationship was found for cannabis use and subclinical positive psychotic experiences, with an increase in these experiences for higher frequencies of use. This, as well as the fact that this relationship still exists after controlling for an elaborate set of confounders, is in agreement with the literature (Zammit *et al.* 2002; Henquet *et al.* 2005; Bossong and Niesink, 2010; McGrath *et al.* 2010; Schubart *et al.* 2010) and adds to the accumulating evidence for cannabis use as a risk factor for psychosis (Van Os *et al.* 2002; Moore *et al.* 2007; Van Os *et al.* 2008; Kuepper *et al.* 2011; Large *et al.* 2011).

Cannabis use at young age

The sample consisted of children aged 12 to 16 years old. Persistence of the association between an early age at cannabis use with subclinical positive psychotic experiences was demonstrated in those who abstained from using cannabis in the last year, and thus used cannabis at least one year before the time of measurement.

There are two possible explanations for this finding; it is in line with the notion of a window of vulnerability (Arseneault *et al.* 2002; Bossong and Niesink, 2010; McGrath *et al.* 2010; Schubart *et al.* 2010), stating that cannabis use during a specific stage of development may lead to persisting psychotic symptoms and eventually even to florid psychosis. Alternatively, the group of discontinued users may pose a selected group of individuals that started early but quit due to adverse effects of cannabis. This would suggest that selection and not a causal relationship explains (part of) the association between cannabis and psychotic experiences.

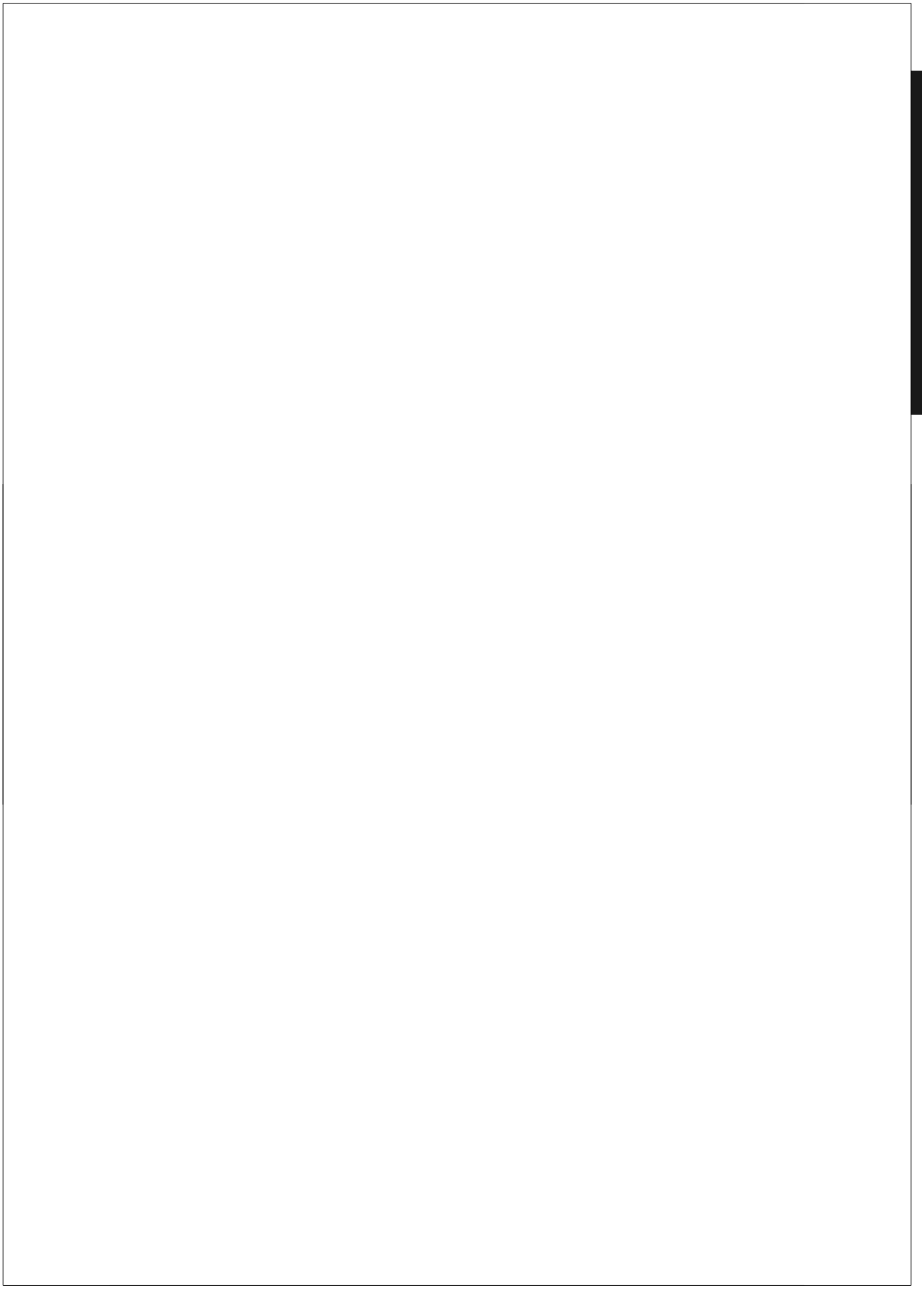
Furthermore, the interaction between age and cannabis use found on the level of psychotic experiences is in line with the findings of Schubart and colleagues (Schubart *et al.* 2010), that a younger age at which cannabis is used is associated with more positive psychotic symptoms. In addition to an association between early onset of use and psychotic experiences later in life, the present study shows that an association also exists for psychotic experiences at present.

Limitations

The present results should be interpreted in context of the strengths and limitations of this study. These data were gathered by self-report, possibly leading to either over- or underreporting of undesirable or illegal behaviour such as cannabis use. However, by administering the questionnaires in school classes and by assuring anonymity, validity and reliability are assumed to improve (Smit *et al.* 2002). Furthermore, studies comparing psychometric and biometric measures of cannabis use (among which urine and hair-tests) show good reliability of self-report measures (Ledgerwood *et al.* 2008; Zaldivar *et al.* 2009). Only 47% of invited schools participated in the study. Since response and non-response schools did not differ with respect to urbanicity and school size, selection bias at this level seems unlikely. The current sample can thus be considered as representative for the Dutch general adolescent population. At class-level, a selection bias could have occurred, missing out truants and those who often miss school due to illness. Since truancy is positively associated to substance use and mental health problems, this bias is more likely to have led to an underestimation of the effect.

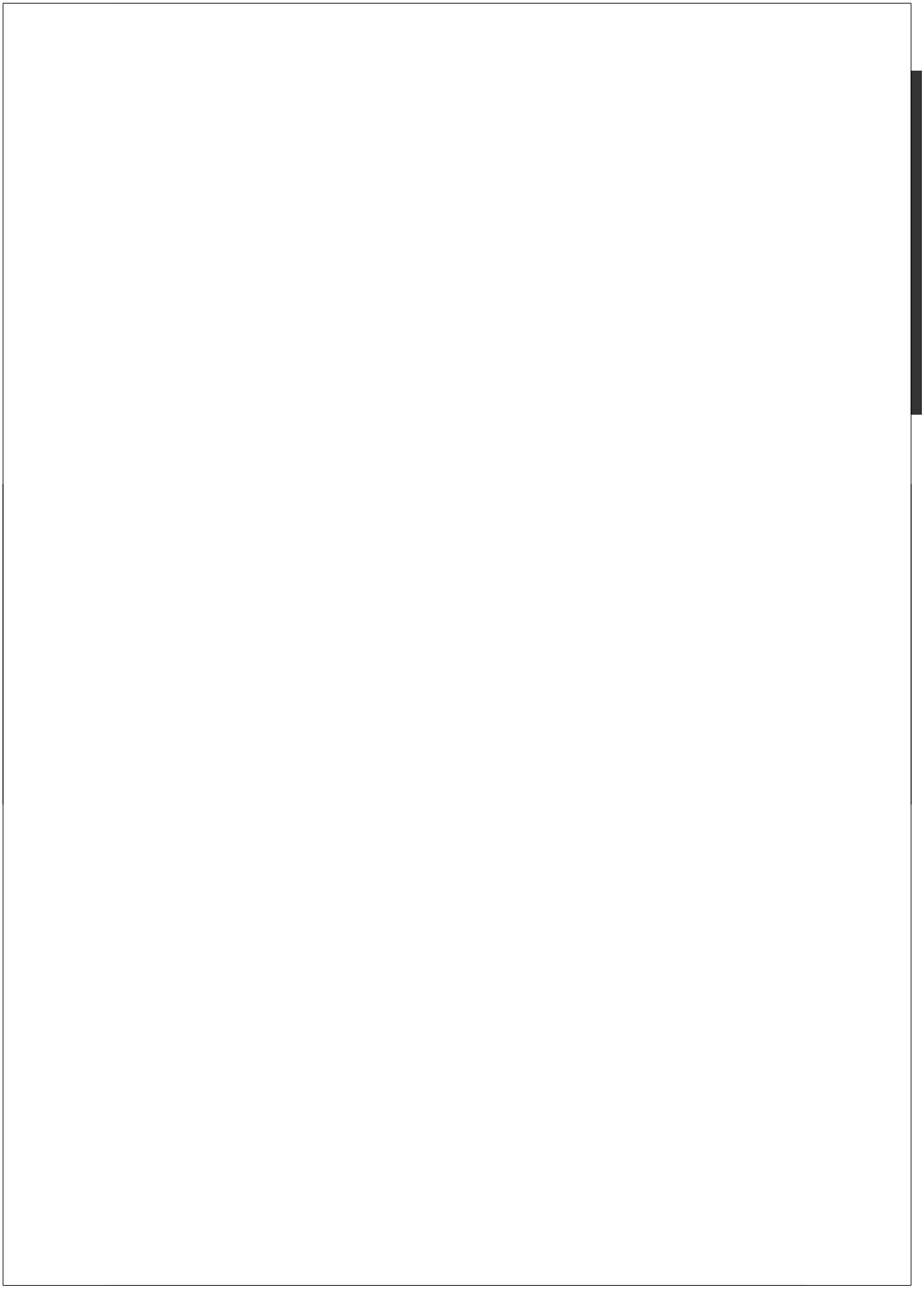
Since the CAPE questionnaire inquires after lifetime psychotic experiences these may be hard to distinguish from acute intoxication effects of cannabis. There is however some evidence that high CAPE scores associated with acute cannabis intoxication are a reflection of psychosis proneness as well. (GROUP researchers, 2011) Also, although measures were available of demographic factors and substance use residual confounding by extensive behavioural and psychopathological factors such as attention-deficit hyperactivity disorder, externalising behaviour and conduct disorder (Monshouwer *et al.* 2006; Karatekin *et al.* 2010; Lee *et al.* 2011; Malcolm *et al.* 2011) can not be ruled out. Future research should include these factors. Furthermore, only frequency of cannabis use during the last year was assessed, whereas a lifetime measure would have been consistent with the time period of the CAPE questionnaire. Also, the lack of information on use of drugs other than cannabis might have led to an overestimation of the found associations. However, since the questions were left out in the 2005 wave due to particularly low prevalence rates in the 2001 wave, this is not likely. A major limitation is that the design of this study is cross-sectional, thus not allowing for a causal inference. Since statistical procedures for correcting for confounders are not infallible and unknown sources of confounding may remain, residual confounding cannot be ruled out. Furthermore, participants were not asked after age of onset of use.

Despite these limitations, the present study is an important addition to the existing literature, since it reveals an enduring association between cannabis use at an early age and subclinical positive psychotic experiences even after abstaining from cannabis for the last year. This calls for more research, which could shed light on the ongoing causality debate evolving around cannabis use and psychotic symptoms. Particularly studies of neuropathological changes resulting from early cannabis use are of interest. Furthermore, specific risk profiles (e.g. low socio-economic status, trauma or psychiatric family history) for psychosis-prone adolescents using cannabis, as well as a threshold-age after which the association between cannabis use and psychosis lessens in strength could prove useful for preventing youngsters from developing psychosis irrespectively whether cannabis use is indeed a causal factor for psychosis or solely an indicator of psychosis-proneness.



Part II

Young Adulthood



4 Moderate cannabis use is a better indicator of poor mental health in women than in men

W.A. van Gastel[1]

J.H. MacCabe[2]

C.D. Schubart[1]

E. van Otterdijk[1]

R.S. Kahn[1]

M.P.M. Boks[1]

Under review

1. Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Department of Psychiatry, HP. B01.206, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands

2. Department of Psychosis Studies, Institute of Psychiatry, King's College London, UK

ABSTRACT

Objective

To explore the relationship between cannabis use, general mental health and potential gender differences.

Method

A cross-sectional online survey of 1,929 young adults aged 18-30 years. Participants reported socio-demographic data, substance use and the Symptom Checklist-90 (SCL-90).

Results

Monthly cannabis use was associated with a higher total score on the SCL-90, both in a crude (OR 1.94, 95% CI: 1.57-2.38) and fully adjusted model (OR 1.48, 95% CI: 1.07-2.03). The association between cannabis and mental health was stronger in women and weekly users, and was independent of age at first use of cannabis.

Conclusion

Moderate cannabis use is associated with general mental health problems in young adulthood. This relationship is independent of age at first use and of other risk factors, and is strongest in women.

INTRODUCTION

Cannabis use is a known risk factor for a range of mental health problems, including psychotic symptoms (Moore *et al.* 2007; Schubart *et al.* 2010; Rossler *et al.* 2012) anxiety and depressive symptoms (Patton *et al.* 2002; Degenhardt *et al.* 2003), attentional dysfunction and poor educational achievement (Ehrenreich *et al.* 1999; ; Horwood *et al.* 2010; Fontes *et al.* 2011). Heavy use and young age at first use is associated with especially high risk for psychiatric disorders (Schubart *et al.* 2010; Rubino *et al.* 2012).

However, less is known about the relationship between cannabis use and general mental health and by which characteristics it is influenced. Hollis and colleagues (Hollis *et al.* 2008) found an association between cannabis use and general mental health problems for adolescents at genetic risk for schizophrenia. Two other population-based studies (Monshouwer *et al.* 2006; van Gastel *et al.* 2012) found such a relationship in a sample of young adolescents from the general population. A focus on more subtle levels of both cannabis intake and mental health problems and on characteristics that interact with cannabis use allows a further exploration of the association of cannabis use and mental health in the general population .

Aim of the Study

In the present study, we investigated the association between moderate cannabis use and general mental health in young adults in the general population. We explored this relationship and the interplay with other characteristics by assessing main and interaction effects of other known risk factors for poor mental health. These factors include age, gender, smoking, alcohol use, foreign ethnicity, level of education, illicit drug use and a family loading for a psychiatric disorder. In addition, we assessed the influence of age at first cannabis use and frequency of current use.

MATERIAL AND METHODS

Participants

Measurements were conducted online, using a research website designed for this purpose (www.CannabisQuest.nl). Participants were recruited via online advertisements on websites, chat-programmes, college intranet, during college introduction periods and in ‘coffee shops’ (shops selling cannabis products). As an incentive, participants had a chance of winning a prize, ranging from a Hawaiian garland and credit for online shopping to a parachute-jump or a laptop computer. The data were collected over the period of March 2006 until April 2011. The questionnaires included socio-demographics, lifestyle, social environment and psychosocial functioning. In order to protect against random

answering and automated answers by internet 'bots', verification questions were applied. All participants gave online informed consent and the study was approved by the ethics committee of the University Medical Center Utrecht.

Measurements

General mental health

To measure general mental health, the SCL-90-R was used (Derogatis *et al.* 1974; Arrindell and Ettema, 2005). This is a widely used screening instrument, for both clinical and research purposes. It consists of 90 items, asking to what extent the respondent felt limited by a psychological problem or symptom of psychopathology during the past week. Scores are on a 5-point Likert scale, ranging from 'not at all' (0) to 'extremely'(4). This results in a score on the total 'Psychoneuroticism' scale, and on nine subscales: Anxiety, Phobic Anxiety, Depression, Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Anger-Hostility, Paranoid Ideation and Psychoticism. The total 'Psychoneuroticism' scale is well validated, and has been shown to predict referral to mental health services two years later in young adults (Ferdinand and Verhulst, 1994). The subscales of Depression, Anxiety and Phobic Anxiety are well validated (Koeter, 1992; Morgan *et al.* 1998). The internal reliability of the total scale and subscales of Anxiety, Phobic Anxiety and Depression subscales are good (Cronbach's alpha ranging from 0.83 for Phobic Anxiety to 0.97 for Psychoneuroticism, (Arrindell and Ettema, 2005)). Therefore, these subscales were used as secondary outcome measures. Scores on the 80th percentile or higher were defined as high (Arrindell and Ettema, 2005), using population norms based on several studies in the general Dutch population between 1992 and 2001 (e.g. (Vendrig *et al.* 2000)). The cut-off scores for a high score were 133 for Psychoneuroticism, 15 for Anxiety, 9 for Agoraphobia and 25 for Depression.

Cannabis Use

Cannabis use was quantified using the item 'how often do you use cannabis?', with answer categories once a year or less (1), yearly (2), monthly (3) or weekly (4). For analysis, this was dichotomised into at least monthly versus less, representing a median split. Subjects were also asked at what age they started using cannabis, categorised into never, after the 15th birthday and before the 15th birthday based on studies showing an increased risk of mental health disorders in users of cannabis before the age of 15 (Fergusson *et al.* 1993; Arseneault *et al.* 2002; Hayatbakhsh *et al.* 2007; Schubart *et al.* 2010; Fontes *et al.* 2011).

Potential confounders

Heavy alcohol use was defined as more than 21 units per week for men and more than 14 for women, according to the Dutch directive for alcohol consumption(de Beer and van de Glind, 2009). For cigarette smoking, a cut-off of daily smoking for at least one month

during the past year was used. Lifetime use of any illicit substance (e.g. amphetamine, khat, opiates, cocaine, GHB and psychedelics) was recorded. Ethnicity was based on the country of birth of grandparents; subjects with two or more grandparents born outside the Netherlands were considered non-native. Education was coded into two levels according to the three educational tracks in Dutch secondary schools and higher education: vocational versus polytechnic and scientific education. Treatment of one or both parents for a mental disorder, including addiction, psychotic and affective symptoms, was also included as a dichotomous indicator.

Data analysis

All analyses were carried out with the statistical package for the social sciences (SPSS 20.0). Listwise exclusion was applied for missing values. First, difference in characteristics between those with a normal or a high total SCL-90 score and was assessed by Chi square tests (and by a Mann-Whitney U test for age). Second, the potential for multicollinearity was investigated by means of bivariate non-parametric correlations (Kendall's $\tau < 0.8$; (Stevens, 2002). Third, logistic regression analyses (yielding odds ratios (OR) with 95% confidence intervals) were carried out, with a high total SCL-90 score (>132) as dependent variable, in crude and fully adjusted models. Age and gender were always included in the adjusted models, other variables only if significant at $p<0.05$ or if their addition to the model changed the odds ratio for cannabis use by 10% or more (Greenland, 1989; Chaves *et al.* 2007). Finally, interactions of cannabis use with confounders were determined. Additional analyses were performed with (1) the subscales of Anxiety, Phobic Anxiety and Depression as outcome measures and (2) with heavy use (at least weekly) as the exposure.

RESULTS

There were 27 missing values for ethnicity, 22 for treatment of parents and 8 for educational track. Listwise exclusion of these resulted in a sample of 1,929 adolescents aged 18-30 years, 947 (49.1%) male. There was one missing value for Phobic Anxiety; for sub-analyses, this case was excluded listwise. Table 1 shows sample characteristics, for the total sample and stratified by total SCL-90 score. About one-third of the total sample (36.5%) had never used cannabis, a further 9.3% less than yearly. 59.0% of subjects with a high SCL-90 score used cannabis during the past month, as opposed to 43.0% in the group with a normal or low total SCL-90 score. Among cannabis users, 50.3% started using between the age of 15 and 17 years; 30.3% started using before the age of 15.

Kendall's τ was below 0.8 for all intercorrelations. Based on the selection criteria, only heavy alcohol use was not included as a confounder in the fully adjusted analysis.

Total score on SCL-90

The ORs for a high total score are shown in table 2. The unadjusted OR for a high total score in moderate cannabis users (as compared to those who used cannabis never or less than monthly) was 1.94 (95% CI: 1.57-2.38, p<0.001). In the fully adjusted model, the OR was reduced to 1.48 (95% CI: 1.07-2.03, p<0.05). Other significant predictors of total score were female gender, regular smoking, non-native grandparents and parental psychiatric disorder. There was a significant interaction between cannabis use and gender, indicating that the association between cannabis use and general mental health problems was strongest in women (p<0.05).

Table 1. Sample characteristics of total study sample (n=1929), stratified by SCL-score. The threshold was set at a score of 133 (Arrindell & Ettema, 2005).

Characteristic	total (n=1929)	Normal score (n=1433)	High score (n=496)
Age in years (mean, sd)	21.6 (2.6)	21.6 (2.6)	21.6 (2.6)
Male gender (n, %)*	947 (49.1%)	731 (51.0%)	216 (43.5%)
Two or more grandparents born abroad (n, %)**	290 (15.0%)	191 (13.3%)	99 (20.0%)
Low level of education (n, %)**	585 (30.3%)	400 (27.9%)	185 (37.3%)
Parent(s) treated for mental health problem (n, %)**	493 (25.6%)	310 (21.6%)	183 (36.9%)
Cannabis use ever (n, %)**	1224 (63.5%)	866 (60.4%)	358 (72.2%)
Monthly cannabis use (n, %)**	929 (48.2%)	561 (43.0%)	368 (59.0%)
Weekly cannabis use (n, %)**	819 (42.5%)	545 (38.0%)	274 (55.2%)
Cigarette smoking (n, %)**	762 (39.5%)	504 (35.2%)	258 (52.0%)
Heavy alcohol consumption (n, %)	116 (6.0%)	81 (5.7%)	35 (7.1%)
Other Illicit substance use ever (n, %)**	707 (36.7%)	488 (34.1%)	219 (44.2%)

** significant difference between the two groups at p<0.01, applying a two-sided Chi square test*

*** significant difference between the two groups at p<0.001, applying a two-sided Chi square test*

Anxiety, phobic anxiety and depression

Cannabis use was significantly associated with Anxiety, Phobic anxiety and Depression, in crude as well as adjusted models. The adjusted OR for cannabis users (versus never and less than monthly) was 1.50 (95% CI: 1.07-2.09, p<0.05) for anxiety. For phobic anxiety this was 1.64 (95% CI: 1.13-2.40, p<0.05), and for depression 1.53 (95% CI: 1.12-2.07, p<0.05). For all three subscales, there was a significant interaction between female gender and cannabis use, showing a stronger association of these measures in women.

Frequency of cannabis use

In a fully adjusted model, the OR for a high total SCL score in heavy cannabis users (at least weekly compared to never or less than weekly) was 1.52 (95% CI: 1.14-2.02, p<0.01).

Table 2. Association between monthly cannabis use and a high total-score on the SCL-90; Odds Ratios (95 % Confidence Interval)

Model	Predictor	Odds Ratio (95 % CI)
Crude	Cannabis use	1.94 (1.57-2.38)**
Fully adjusted	Cannabis use	1.48 (1.07-2.03)*
	Age at first use	1.48 (1.12-1.96)*
	Age	0.98 (0.94-1.02)
	Female Gender	1.54 (1.24-1.92)**
	Regular smoking	1.37 (1.03-1.81)*
	Two or more grandparents born abroad	1.34 (1.01-1.78)*
	Low education	1.20 (0.95-1.52)
	Illicit drug use (ever)	0.87 (0.65-1.16)
	Parent treated for a psychiatric disorder	1.82 (1.45-2.29)**

ns: non-significant
** significant at p<0.05*
*** significant at p<0.001*

DISCUSSION

In a large sample of young adults aged 18 to 30 years old, we found that monthly cannabis use was associated with poor general mental health, independent of age at onset of use and of other risk factors. The only modifier for this effect was gender: the association was strongest in women. Previous studies investigated higher levels of cannabis use and a more severe level of mental health problems (Schubart, 2011), specific symptom dimensions (see (Degenhardt *et al.* 2003; Moore *et al.* 2007) for reviews) or were restricted to (early) adolescence (Monshouwer *et al.* 2006; Hollis *et al.* 2008).

Frequency of cannabis use

In the present study, we found that the odds ratio for poor mental health was elevated for moderate (at least monthly) cannabis users, and slightly more so for heavy (at least weeky) users. This is in line with dose-response effects found for the association between cannabis use and a range of mental health outcomes of varying severity, including psychotic-like experiences (Henquet *et al.* 2005; Moore *et al.* 2007; Schubart *et al.* 2010; Schubart *et al.* 2011), externalising problems (Monshouwer *et al.* 2006; Goodman, 2010), depression (Brook *et al.* 1998) and psychiatric hospitalization (Schubart *et al.* 2011). Although dose-response relationships are consistent with a causal relationship, empirical evidence has shown that these associations are not necessarily causal (Smith *et al.* 1992; Macleod

et al. 2002; Macleod *et al.* 2004). Furthermore, the difference between the corrected odds ratios for monthly and weekly use were rather small in this study. Of note in this respect is that tobacco smoking showed a comparably strong association with mental health problems as cannabis use in the current study, in line with previous findings for specific symptoms dimensions (Brook *et al.* 1998; Degenhardt *et al.* 2001; Degenhardt and Hall, 2001; Saha *et al.* 2011; van Gastel *et al.* 2012).

Age at first use

Cannabis use before the age of 15 years has been indicated as a risk factor for psychotic-like experiences (Schubart *et al.* 2010), schizophreniform psychosis (Arseneault *et al.* 2002), anxiety and depression (Hayatbakhsh *et al.* 2007), poor executive functioning (Fontes *et al.* 2011) and conduct disorder (Fergusson *et al.* 1993). The current results show that early onset of cannabis use is also associated with poor general mental health, independent of current cannabis use and other risk factors. It has been suggested that this could be due to an adverse impact on the development of the endo-cannabinoid and/or dopaminergic system (Bossong and Niesink, 2010; Rubino *et al.* 2012), although confounding remains a possibility.

Cannabis use and female gender

We found an interaction for gender and cannabis use, indicating that the association between cannabis use and poor mental health is strongest in women. This is in line with findings in other domains: Compton and colleagues (Compton *et al.* 2009) found that women who used cannabis had an increased risk of onset of psychosis versus men who used cannabis and Pedersen and colleagues (Pedersen *et al.* 2001) found a similar interaction for conduct disorder, with conduct disorder preceding cannabis use. Also, Lev-Ran and colleagues (Lev-Ran *et al.* 2012) found that the decrease in self-reported mental quality of life associated with cannabis used was stronger in women. Our study adds to the literature that this interaction is also apparent for moderate cannabis use, with poor general mental health as an outcome.

Since cannabis use is less prevalent in women (in this study, 36.7% of women indicated monthly cannabis use, versus 60.1% of men), it could be argued that women who smoke cannabis are more deviant than men who use cannabis. Risk factors for mental health problems may therefore accumulate in female cannabis users, for example psychiatric familial liability (Mortensen *et al.* 1999), low socio-economic status (Holstein *et al.* 2009; McLaughlin *et al.* 2011), status of ethnic minority (Veling and Susser, 2011; Selten *et al.* 2012; Termorshuizen *et al.* 2012), and traumatic experiences (Konings *et al.* 2012). In addition, cannabinoids have been found to have diverse effects in men and women (for

a review, see (Fattore and Fratta, 2010)). In the short term, cannabis use is associated with more frequent symptoms of depression and anxiety in women, thus making a gender specific long-term relationship with these symptoms plausible. Research into a neurobiological basis for gender-based differences in the effects of cannabinoids points towards differences in distribution of muscle- and fat tissue, and as a special role for gonadal hormones (Fattore and Fratta, 2010).

Cannabis use, Depression and Anxiety

Monthly cannabis use was associated with the subscales of Anxiety, Phobic Anxiety and Depression in the present study, also after adjusting for confounders. These results are consistent with previous longitudinal studies that have mainly provided evidence for cannabis causing anxiety and depressive symptoms (e.g. (Bovasso, 2001; Fergusson *et al.* 2002; Patton *et al.* 2002; Degenhardt *et al.* 2003; Hayatbakhsh *et al.* 2007)).

Underlying mechanisms

A part from a causal association, two alternative explanations are frequently advanced for associations between cannabis use and mental health problems: confounding and self-medication (Kendler *et al.* 1993; Degenhardt *et al.* 2001; Gregg *et al.* 2007; Swendsen *et al.* 2011; van Leeuwen *et al.* 2011). Although a meta-analysis (Moore *et al.* 2007) reported an approximately 1.5-fold increased risk of depressive outcomes for cannabis users, the authors considered that the included studies did not sufficiently account for confounding and the possibility of reverse causation.

Confounding

Socio-demographic factors that might confound the association between cannabis use and mental health outcomes include lower socioeconomic group, poor academic achievement, male gender, other substance misuse (particularly tobacco smoking) and migration (Monshouwer *et al.* 2006; Selten *et al.* 2012; Termorshuizen *et al.* 2012; van Gastel *et al.* 2012). It is also plausible that biological factors may confound the association – for example, some genetic risk factors for psychosis may also predispose to cannabis use. Confounding by early or genetic factors is supported by the recent finding of smaller orbitofrontal cortex volumes at age 12 years, preceding initiation of cannabis use by age 16 years (Cheetham *et al.* 2012). Although we have adjusted for potential confounders as much as possible, residual confounding remains a possibility. Factors that may confound the association, but that were not measured, include urbanicity, socio-economic status, social support, household composition(Monshouwer *et al.* 2006; van Gastel *et al.* 2012) and traumatic experiences (Konings *et al.* 2012; Larsson *et al.* 2012; O'Hare *et al.* 2012).

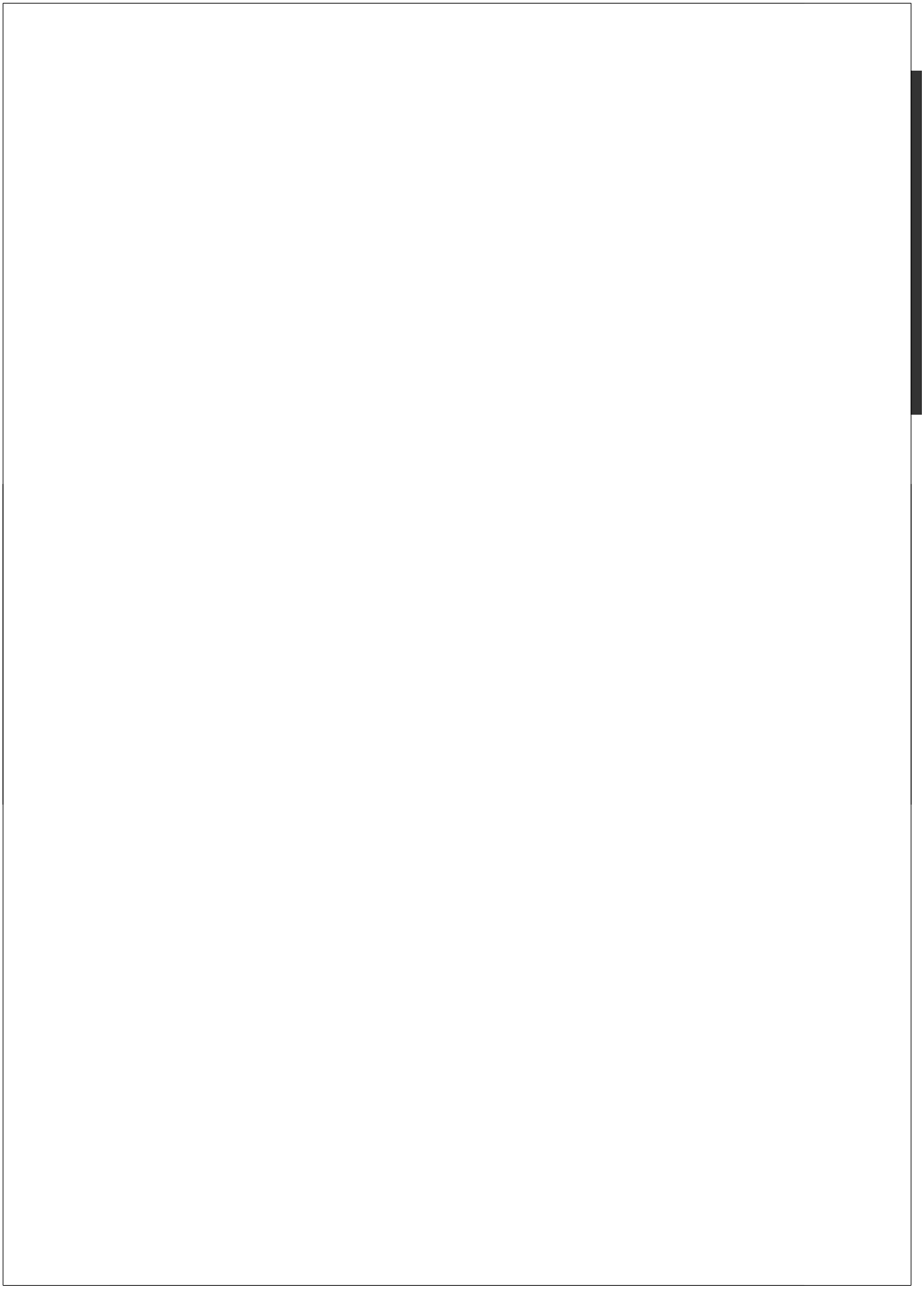
Reverse causality

There is some evidence for anxiety and depression leading to cannabis use, in an effort to self-medicate (Buckner *et al.* 2007; Wittchen *et al.* 2007; Fox *et al.* 2011; Buckner *et al.* 2012). In a cross-sectional study it is not possible to exclude self-medication as an explanation.

Limitations

A major limitation is that the study is cross-sectional, precluding firm conclusions regarding causality. Furthermore, our data were gathered by self-report via the internet, potentially leading to either over- or underreporting of undesirable behaviour such as cannabis use. However, studies comparing psychometric and biometric measures of cannabis use (among which urine and hair-tests) show good reliability of self-report measures (Ledgerwood *et al.* 2008; Zaldivar *et al.* 2009), and recent studies have shown that the internet is a suitable instrument for scientific research (Meyerson and Tryon, 2003; Gosling *et al.* 2004; Balter *et al.* 2005; Ekman *et al.* 2006; Vleeschouwer *et al.* 2012). Our sample may not be representative of the general population, and sampling from universities and coffee shops may have resulted in a sample enriched for students and cannabis users. Another potential disadvantage of online surveys is that the participants cannot be screened for intoxication; the acute effects of cannabis might therefore have influenced the scores of the SCL questionnaire.

Despite these limitations, the present study is an important addition to the existing literature, since it reveals that moderate cannabis use is independently associated with general mental health. Although the (causal) nature of the association remains unclear, cannabis use can be viewed as an indicator of risk for poor mental health, even when used in moderate frequency, and especially in women.



5 Cannabis use at young age is associated with psychotic experiences

C.D. Schubart[1]

W.A. van Gastel[1]

E.J. Breetvelt[1]

S.L. Beetz[1]

R.A. Ophoff[1,2,3]

I.E.C. Sommer[1]

R.S. Kahn[1]

M.P.M. Boks[1]

Psychological Medicine (2010) **7**, 1-10

1. Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Department of Psychiatry, The Netherlands.

2. UCLA Center for Neurobehavioral Genetics, Los Angeles, CA, USA.

3. Dept of Medical Genetics, University Medical Centre Utrecht, The Netherlands.

ABSTRACT

Background

Cannabis use is associated with psychosis and a range of subclinical psychiatric symptoms. The strength of this association depends on dosage and age at first use. The current study investigates whether level of cannabis exposure and starting age are associated with specific profiles of subclinical symptoms.

Methods

We collected cross-sectional data from a young adult population sample by administering an online version of the Community Assessment of Psychic Experiences (CAPE). Cannabis exposure was quantified as the amount of euros spent on cannabis per week and the age of initial cannabis use. The primary outcome measure was the odds ratio to belong to the highest 10% of scores on the total CAPE and the positive-, negative- and depressive symptom dimensions.

Results

In 17,698 adolescents (mean age 21.6 SD 4.2), cannabis use at age 12 or younger was strongly associated with a top 10% score on psychotic experiences (OR: 3.1, 95%CI 2.1 – 4.3) and to a lesser degree with negative symptoms (OR: 1.7, 95%CI 1.1 – 2.5). The odds ratio of heavy users (>€25/week) for negative symptoms was 3.4 (95%CI 2.9 – 4.1), for psychotic experiences 3.0 (95%CI 2.4 – 3.6), and for depressive symptoms 2.8 (95%CI 2.3 – 3.3).

Conclusions

Early start of cannabis use is strongly associated with subclinical psychotic symptoms and to a lesser degree with negative symptoms, while smoking high amounts of cannabis is associated with increased levels of all three symptom dimensions: psychotic, negative and depressive. These results support the hypothesis that the impact of cannabis use is age specific.

INTRODUCTION

Cannabis is the most widely used illicit substance in the world. The number of users is increasing and is estimated to range from 142.6-190.3 million worldwide, with the highest prevalence in young people (United Nations Office on Drugs and Crime, 2009). Although in the U.S. and Canada the overall lifetime prevalence of cannabis use is around 46%, in 18- to 24-year-olds the prevalence is 70% (Adlaf *et al.* 2005; SAHMSA, 2007). A recent U.S. national survey (Johnston *et al.* 2009) showed that the lifetime prevalence among 13-year-old children is as high as 15%. In Europe, on average one in three adolescents between 15–24 years has ever used cannabis (European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA), 2008). Extensive use of cannabis by young individuals has lead to concerns regarding potential impact on population mental health. Numerous large longitudinal studies observed an independent effect of cannabis on the development of psychotic disorders, for review see (Moore *et al.* 2007). However, the impact of cannabis use is not restricted to clinically manifest psychotic disorders. In the general population, cannabis use is dose dependently associated with subclinical psychiatric symptoms such as psychotic experiences and negative symptoms (Arseneault *et al.* 2002; Fergusson *et al.* 2003; Verdoux *et al.* 2003; Stefanis *et al.* 2004; Konings *et al.* 2008; Miettunen *et al.* 2008; Hides *et al.* 2009). Three of these studies report that these associations are stronger in younger subjects (Arseneault *et al.* 2002; Fergusson *et al.* 2003; Stefanis *et al.* 2004). A dose dependent relationship between the amount of cannabis exposure and subclinical symptoms suggests that the level of exposure to tetrahydrocannabinol (THC), the main psychoactive component of cannabis (Mechoulam and Gaoni, 1965), determines this relationship. The association between age of initial cannabis use and subclinical symptoms is less straightforward. One possible explanation is that individuals who are prone to psychotic experiences are more inclined to smoke cannabis at an early age. However there is also evidence suggesting that there is a window of vulnerability to cannabis exposure that explains the increased association between early use and psychiatric symptoms (Arseneault *et al.* 2002; Fergusson *et al.* 2003; Stefanis *et al.* 2004). Animal studies for instance show that exposure to THC during critical periods of brain maturation, such as early puberty, impacts on the development of several neurotransmitter systems (Trezza *et al.* 2008), suggesting that THC interferes with crucial processes in brain development. It is possible that the pathophysiological mechanisms underlying the associations with amount of use and the association with age of first use are distinct. If first exposure to cannabis early in life interferes with specific developmental processes, this may be reflected in a specific profile of subclinical psychiatric symptoms. A more detailed study of the association between cannabis use and subclinical psychiatric experiences may therefore reveal how these different aspects of cannabis use impact on subclinical psychiatric experiences.

Since several studies show that a high score on self-reported psychotic symptoms predict an increased risk of a psychotic disorder later in life (Chapman *et al.* 1994; Poulton *et al.* 2000; Hanssen *et al.* 2005; Wiles *et al.* 2006; Yung *et al.* 2009), it is particularly interesting to study the relationship between cannabis use and high scores of these subclinical psychiatric experiences. We here report a study on the association between the amount of cannabis use and the age of initial cannabis use and top 10% scores in three symptom dimensions of self-reported psychiatric experiences in a large population sample.

METHODS

Participants

Participants were recruited using a project website mainly targeting Dutch speaking adolescents and young adults (18-25 years). Recruitment strategies included cooperation with more than 100 colleges, universities and youth centres that were willing to advertise for this study on their intranet and the use of online commercial advertisement products (i.e. banners and text links). The chance to win an Apple iPod ™ or a Nintendo Wii ™ was used as an incentive. Participants answered questions regarding their cannabis use, filled out the Community Assessment of Psychic Experiences (CAPE)(Konings *et al.* 2006) questionnaire and provided their age, educational level and contact details. Submitting data anonymously was not possible. Every month approximately 670 visitors filled out our web based questionnaires between June 2006 and February 2009. This resulted in 21,838 participants. The assessment included two verification questions to protect against random answers. Participants that failed to correctly fill out the verification questions were excluded. To increase the homogeneity of the sample participants that indicated to be younger than 10 years or older than 60 years of age were excluded. After exclusion of these individuals, 17,698 participants remained (81% of 21,838). This study was approved by the UMC Utrecht medical ethical commission and all participants gave online informed consent.

Assessments

As a measure of subclinical psychiatric experiences, the CAPE questionnaire was used. The CAPE is a 42-item, self-rating instrument and has a three-factor structure of 20 questions in the positive symptom dimension (delusional thinking, verbal- and visual hallucinations), 14 in the negative and 8 in the depressive dimension. It measures frequency as well as distress associated with these experiences. The questionnaire has discriminative validity for the different symptom dimensions in individuals from the general population (Stefanis *et al.* 2002; Hanssen *et al.* 2003; Konings *et al.* 2006)(http://www.cape42.homestead.com/). The primary outcome measure was the odds ratio to belong to the highest 10% of total- and dimensional scores (positive, negative and depressive). Web-based

questionnaires are reliable for epidemiologic research purposes, especially in settings in which internet access is high (Ekman *et al.* 2006b), as is the case in The Netherlands where 99% of all adolescents use the internet on a daily basis (CBS Statistics Netherlands, 2009).

Cannabis measures

In the Netherlands, THC-concentration and cannabis market value are highly correlated in marijuana ($r=0.365$, $p < 0.001$) and in hashish ($r=0.719$, $p < 0.001$)(Niesink *et al.* 2009). Therefore, we assessed the amount of euros (€) spent on cannabis per week in the last month, as a proxy measure of exposure to THC. For reference, prices range from €4.30 for one gram of imported marijuana with an average THC percentage of 5.5% to €15, - per gram of Dutch hashish with an average THC concentration of 33.3% (Trimbos Institute, 2008). Participants were asked how many euros equivalent of cannabis they use per week and to choose one of the following classes; 1) cannabis naïve individuals who indicated never to have used cannabis; 2) participants using cannabis incidentally or spending less than 3 euros per week; 3) individuals spending between 3-10 euros per week on cannabis; 4) participants spending between 10-25 euros per week; and 5) individuals spending more than 25 euros per week on cannabis. All categories (except for the first two groups) applied to the last month or longer. The initial age of cannabis use was categorized by asking participants which of the following five subgroups describes their cannabis use history; 1) participants who started to use before the age of 12 years; 2) first cannabis use between 12 and 15 years; 3) between 15 and 18 years; 4) between the age of 18 to 20 years; and 5) individuals that started to use after their 20th birthday.

Concomitant drug use

As part of another ongoing study, the first 13,000 participants were asked to fill out a number of additional questionnaires on various topics such as concomitant drug use. A sub sample of 816 participants completed a digital version of the drug use section of the Composite International Diagnostic Interview (CIDI) (Robins *et al*., 1988). This sub sample did not differ significantly from the total sample in terms of cannabis use, CAPE score, age, sex and educational level.

Statistical analysis

Firstly, we analyzed the relation between the weekly amount of money spent on cannabis and having a top 10% score on the different symptom dimensions. Odds Ratios (ORs) and their 95% confidence intervals (95% CI) for the amount of cannabis use were calculated using logistic regression, with a dichotomized score on the total CAPE and the three dimensions of the CAPE as the dependent variable and THC exposure categories as the independent variables. Cannabis naïve individuals were used as the reference group.

Corrected ORs and their 95%CI were calculated with additional adjustment for age, gender and level of education. Secondly, in the subgroup that used cannabis, ORs and their 95% CI for initial age of cannabis use were calculated using logistic regression, with a dichotomized score on the total CAPE and the three dimensions of the CAPE as the dependent variable and age categories as the independent variables. The age category of modal initial age (15 -18 years) was used as reference group to assess the risks of early use (i.e. before the age of 12 years) compared to a more common starting age of cannabis use. Corrected ORs and their 95%CI were calculated with additional adjustment for age, gender and level of education.

To assess the sensitivity of our results to selection bias, we performed two additional analyses. We estimated the impact of a hypothetical decrease in the number of heavy users (>25€/week) with total CAPE score in the top10% of the distribution. The same calculation was performed considering a hypothetical decrease of individuals with a top 10% CAPE score that started to use cannabis at or before the age of 12. Randomly, a predefined fraction of the heavy or young users was excluded and the association between cannabis use and a top 10% CAPE score was estimated in the remaining participants. This procedure was repeated 1,000 times for each predefined fraction and odds ratios and their confidence intervals were pooled using Rubin's rule (Rubin, 1987).

Additional analyses were performed to assess the influence of lifetime concomitant drug use using the logistic regression model as described before with an extra indicator for concomitant use. Data were analyzed using R for Windows, version 2.9.1 (2005).

RESULTS

A total of 17,698 subjects participated in our study. The mean age in our sample was 21 years (SD:4.2) and 51% was male. The educational level of the sample was comparable to the Dutch population in this age group (CBS Statistics Netherlands, 2008). No educational diploma had been attained by 0.1% of the sample, secondary school was the highest educational attainment in 50.4%, 34.3% had a non-academic post-secondary school diploma and 8.3% had an academic diploma. Table 1 presents further characteristics of the sample.

Table 1. Participant characteristics

	Total Group	Non-Users	Users
Number of participants	17,698	5,842	11,856
Gender (% male)	51	32.9	57
Mean age (SD)	21.6 (4.2)	21.0 (3.8)	22.0 (4.3)
Total cape score mean (SD)	101.3 (30,1)	99.1 (27.2)	102.4 (31.4)
Positive dimension mean (SD)	38.4 (12.7)	37.3 (11.3)	38.9 (13.3)
Negative dimension mean (SD)	39.0 (14.1)	37.8 (12.9)	39.6 (14.6)
Depressive dimension mean (SD)	23.9 (8.7)	24.0 (8.1)	23.9 (8.9)

Initial age of cannabis use

Individuals who started to use cannabis before the age of 12 years, had an adjusted odds ratio of 3.1 (95%CI 2.1 – 4.3) for the highest 10% of scores on psychotic experiences compared to participants with a modal starting age (15-18 years). Starting to use between the age of 12 and 15 years resulted in an adjusted odds ratio of 1.2 (95%CI 1.0 – 1.3). Initial age of cannabis use after 18 years was not associated with an increased score on psychotic experiences. An increase of experiences in the negative symptom dimension was associated with using cannabis before the age of 12 (OR: 1.7 (95%CI 1.1 – 2.5)) and also before the age of 15 (OR: 1.1 (95%CI 1.0 – 1.3)). Using cannabis for the first time after the age of 18 years was not associated with an increased OR for the negative symptom dimension. In contrast, depressive symptoms were not associated with a young initial age of cannabis use. However, individuals who started after the age of 20 years experienced more depressive symptoms than the reference group (OR: 1.4, 95%CI: 1.0 – 1.8)). Figure 1 depicts adjusted odds ratios for five categories of initial age of cannabis use and a psychotic experiences score in the top 10% in the three symptom dimensions. Table 2 shows all adjusted odds ratios and their 95% confidence intervals for top 10% scores on the total CAPE and its three symptom dimensions.

Table 2. Full-model odds ratios with 95% confidence interval boundaries for the top 10% scores on the three symptom dimensions and the total scores of psychiatric experiences. Significant OR's are bold.

Amount of €/week OR for a top10% total CAPE score	**Corrected OR***	**Lower 95% CI**	**Upper 95% CI**
Cannabis naïve (N=5842) **	1.00	-	-
0 to 3 € (N=6,432)	0.96	0.82	1.13
3 to 9 € (N=1,814)	**1.46**	**1.21**	**1.76**
9 to 25 € (N=2,106)	**2.00**	**1.68**	**2.38**
>25 € (N=1,504)	**3.54**	**2.94**	**4.26**
Amount of €/week OR for top10% positive dimension score	**Corrected OR***	**Lower 95% CI**	**Upper 95% CI**
Cannabis naïve (N=5842) **	1.00	-	-
0 to 3 € (N=6,432)	0.98	0.84	1.15
3 to 9 € (N=1,814)	**1.72**	**1.44**	**2.06**
9 to 25 € (N=2,106)	**1.96**	**1.65**	**2.33**
>25 € (N=1,504)	**2.95**	**2.44**	**3.56**
Amount of €/week OR for top10% negative dimension score	**Corrected OR***	**Lower 95% CI**	**Upper 95% CI**
Cannabis naïve (N=5842) **	1.00	-	-
0 to 3 € (N=6,432)	0.95	0.81	1.11
3 to 9 € (N=1,814)	**1.34**	**1.11**	**1.62**
9 to 25 € (N=2,106)	**2.05**	**1.74**	**2.42**
>25 € (N=1,504)	**3.43**	**2.87**	**4.1**
Amount of €/week OR for top10% depressive dimension score	**Corrected OR***	**Lower 95% CI**	**Upper 95% CI**
Cannabis naïve (N=5842) **	1.00	-	-
0 to 3 € (N=6,432)	1.01	0.87	1.16
3 to 9 € (N=1,814)	**1.26**	**1.05**	**1.52**
9 to 25 € (N=2,106)	**1.63**	**1.37**	**1.94**
>25 € (N=1,504)	**2.75**	**2.28**	**3.32**

Table 2. Continued

Initial age OR for a top10% total CAPE score	**Corrected OR****	**Lower 95% CI**	**Upper 95% CI**
>20 (N=545)	1.18	0.90	1.55
18-20 (N=1,909)	0.94	0.78	1.13
15-18 (N=5,722) **	1.00	-	-
12-15 (N=3,426)	**1.16**	**1.01**	**1.32**
<12 (N=154)	**1.82**	**1.23**	**2.70**
Initial age OR for a top10% positive dimension score	**Corrected OR****	**Lower 95% CI**	**Upper 95% CI**
>20 (N=545)	1.06	0.76	1.48
18-20 (N=1,909)	0.84	0.69	1.01
15-18 (N=5,722) **	1.00	-	-
12-15 (N=3,426)	**1.15**	**1.01**	**1.31**
<12 (N=154)	**3.05**	**2.14**	**4.34**
Initial age OR for top10% negative dimension score	**Corrected OR****	**Lower 95% CI**	**Upper 95% CI**
>20 (N=545)	1.22	0.89	1.66
18-20 (N=1,909)	1.02	0.85	1.22
15-18 (N=5,722) **	1.00	-	-
12-15 (N=3,426)	**1.14**	**1.00**	**1.30**
<12 (N=154)	**1.66**	**1.13**	**2.45**
Initial age OR for top10% depressive dimension score	**Corrected OR****	**Lower 95% CI**	**Upper 95% CI**
>20 (N=545)	**1.35**	**1.01**	**1.80**
18-20 (N=1,909)	0.95	0.79	1.14
15-18 (N=5,722) ***	1.00	-	-
12-15 (N=3,426)	1.04	0.91	1.20
<12 (N=154)	1.24	0.80	1.94

** Adjusted for age, gender, level of education and of onset age of cannabis consumption in the total study population.*

*** Adjusted for age, gender, level of education and of onset age of cannabis consumption in the cannabis users.*

**** Reference group in logistic regression analysis.*

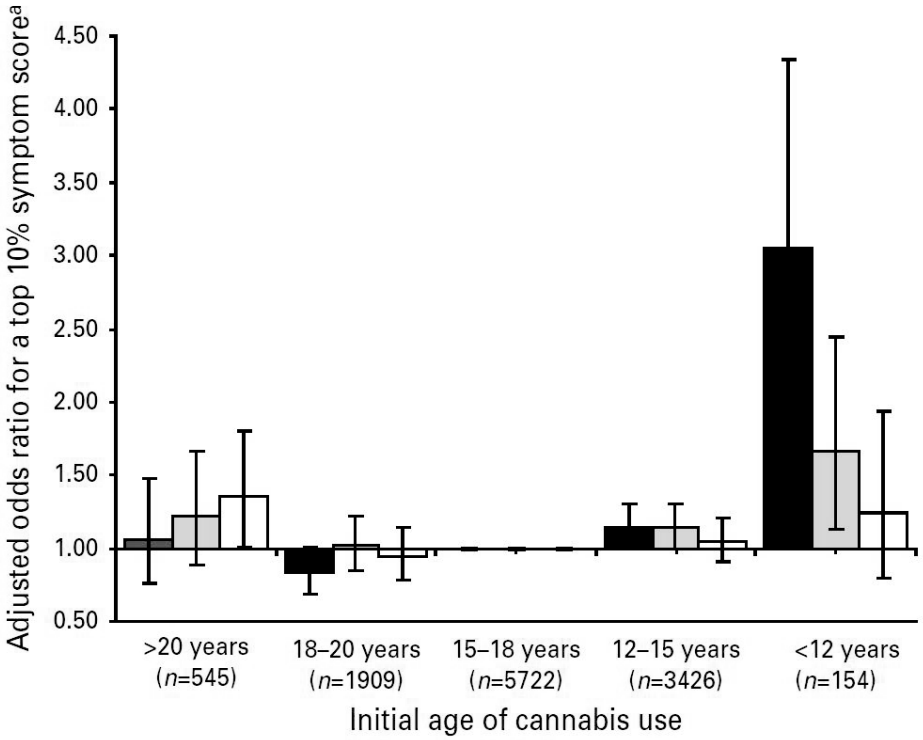


Figure 1. Subclinical psychiatric symptoms and initial age of cannabis usewith the modal starting age category (15-18 years) as reference group (Total N=11,856).
** Adjusted for age, gender, educational level and amount of cannabis use.*

Quantity of weekly cannabis use

Analyzing the odds ratios associated with quantity of use, we found that the odds ratio for a top 10% score on psychotic experiences increases with the amount of cannabis that subjects indicate to use weekly. Odds ratios for a top 10% score on psychotic experiences range from 1.7 (96%CI 1.1 – 2.1) in users consuming €3 to €9 weekly to 3.0 (95%CI 2.4 – 3.6) in heavy users (>€25). Likewise, quantity of use was associated to negative symptoms with adjusted odds ratios ranging from 1.3 (95%CI 1.1 – 1.6) in participants who used between €3 and €9 per week to 3.4 (95%CI 2.9 – 4.1) in individuals who consume a weekly equivalent of more than €25. Computation of the adjusted odds ratios for a top 10% score on depressive symptoms produced an odds ratio of 1.3 (95%CI 1.1 - 1.5) in participants that used a weekly cannabis equivalent of €3 to €9 euros. Spending more than 25 euros per week on cannabis was associated with an adjusted odds ratio of 2.8 (95%CI 2.3 – 3.3) in this symptom dimension. Cannabis naïve subjects were used as the reference group

in these analyses. All odds ratios are listed in table 2. Figure 2 depicts the adjusted odds ratios per category of weekly amount of use for a top 10% score on each of the three symptom dimensions.

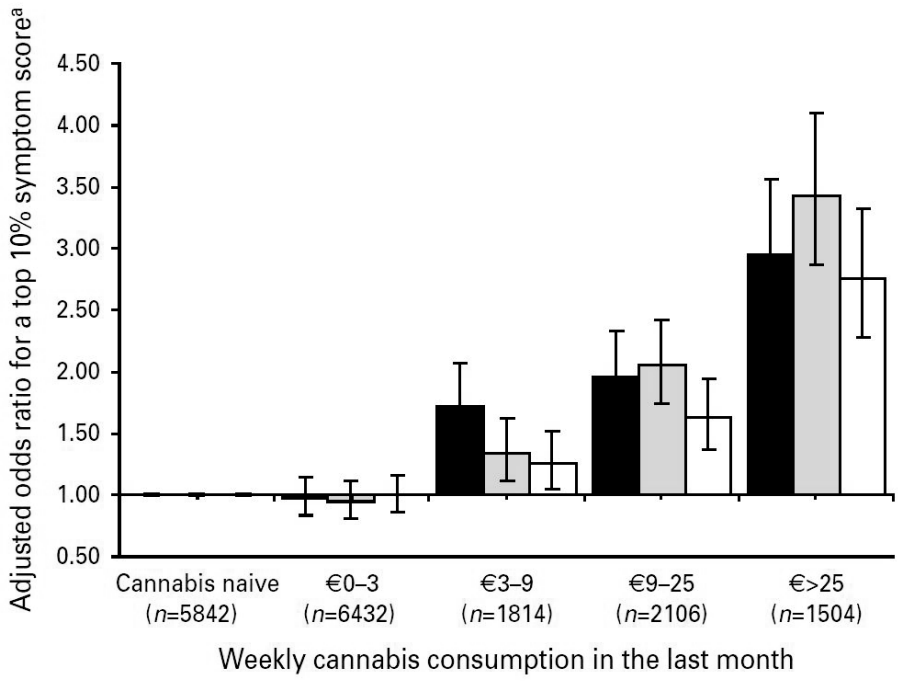


Figure 2. Subclinical psychiatric symptoms and weekly amount of use during the last month or longer with the cannabis naïve group as reference (Total N=17,698).
** Adjusted for age, gender and educational level.*

Concomitant drug use

In the subsample in which information on concomitant drug use was available (N=816, not shown in tables), we performed an additional logistic regression analysis to assess the impact of lifetime use of other drugs than cannabis on the presented associations. In the group that used more than €25 worth of cannabis weekly, the odds ratio for a top 10% total CAPE score was 14.35 (95% CI 3.3 – 61.6) after adjustment for concomitant drug use. In this model, the odds ratio for a top10% CAPE score associated with concomitant drug use was 3.1 (95%CI 0.8 – 12.7). The odds ratio for a top 10% total CAPE score in participants who started before the age of 12 years was 2.3 (95%CI 0.6 – 8.7) after adjustment for concomitant use. In the model for age of initial use, the odds ratio associated with the

presence or absence of concomitant drug use was 0.9 (95%CI 0.4 – 2.0). A wide confidence interval and strong collinearity between concomitant drug use and an early initial age of cannabis use (r>0.8), indicate a weak statistical model.

Analysis of sensitivity to selection bias

It is conceivable that subjects experiencing psychiatric symptoms were more likely to participate in our study. If such selection was simultaneously skewed towards those that started to use cannabis before the age of 12 years or use more than 25€ per week, selection bias could have influenced the results. To quantitatively assess the sensitivity of the current design to such selection bias, we calculated the impact of a decrease in the number of participants with a high total score on psychiatric experiences (total CAPE) and i) a history of initial cannabis use before the age of twelve years or ii) having used a cannabis equivalent of more than €25 during the last month. These analyses indicate that the odds ratio would remain significant until 20% of participants with a high score on psychiatric experiences who also started to use cannabis before the age of 12 years are excluded from the analysis. Exclusion of 63% of participants with a high score on psychiatric experiences and heavy use (>€25/week) over the last month would render the association non-significant. The adjusted odds ratios for several hypothetical steps can be found in table 3.

Table 3. Selection Bias Analysis, showing hypothetical adjusted odds ratios after exclusion of different proportions of participants with a total CAPE score in the top 10% of the distribution and 1) initial age of use before the age of 12 years or 2) heavy use (>€25/week) of cannabis.

proportion of excluded participants	**adjusted odds ratio for onset age <12** *	**95%CI**		**adjusted odds ratio for amount >25€/week** *	**95%CI**	
		lower	upper		lower	upper
0	1.82	1.23	2.70	3.54	2.94	4.26
0.1	1.64	1.09	2.46	3.16	2.61	3.83
0.2	1.45	0.95	2.21	2.79	2.29	3.40
0.3	1.27	0.82	1.98	2.43	1.98	2.98
0.4	1.09	0.68	1.74	2.07	1.67	2.56
0.5	-	-	-	1.70	1.36	2.13
0.6	-	-	-	1.35	1.06	1.71

* *adjusted for age, gender and level of education.*

DISCUSSION

We investigated the association between initial age and amount of cannabis use and psychiatric experiences in three symptom dimensions (positive, negative and depressive) in a sample of over 17,500 participants with a mean age of 21 years. We found that young initial age of cannabis use is strongly associated with current psychotic experiences. Although young cannabis users also had significantly increased odds ratios of experiencing more negative symptoms, the odds ratio for psychotic experiences was almost twice as high. Depressive symptoms were not associated with early onset of cannabis use. We also found that the amount of cannabis use is equally strongly related to positive-, negative- and depressive symptoms. Finally, our results show that moderate cannabis use and onset of cannabis use after the age of 18 years, did not increase the odds for having subclinical psychiatric experiences.

Initial age of cannabis use

An age-related association between cannabis use and subclinical symptoms was described before. However, from these studies it is not possible to identify the most vulnerable age group (Arseneault *et al.* 2002; Fergusson *et al.* 2003; Stefanis *et al.* 2004). As these studies were cross-sectional too, they also do not allow causal inference. Therefore it is possible that this association reflects an increased propensity of young people with psychotic experiences to commence cannabis use. Another alternative explanation of these findings could be higher cumulative exposure to cannabis of early users, this hypothesis assumes that subjects that started at a young age continued to use cannabis in a certain pattern until present date, however detailed information on the pattern of use from onset to current use was not available. The disproportional level of psychotic symptoms among young cannabis users, compared to the more balanced profile of psychiatric symptoms that is associated with current quantity of cannabis use, is not easily explained by reverse causality or higher cumulative exposure. However, given the cross-sectional nature of the data, do not allow such causal inference.

An alternative hypothesis is that increased vulnerability to THC during critical phases of brain maturation, as in early puberty, is reflected in a specific association between psychotic experiences and a young initial age of THC exposure. Such a window of vulnerability in early puberty is supported by a recent cohort study that showed that early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults (McGrath *et al.* 2010) and by experimental studies of the endocannabinoid system (ECN).

The ECN plays an important role in brain organization during prenatal development and early puberty (Chevaleyre *et al.* 2006). Exposure to high levels of exo cannabinoids, such as THC, can disrupt neuronal signalling and might interfere with the activity of the endocannabinoid system during stages of high neuronal plasticity (Lewis, 1997; Trezza *et al.* 2008). In animal models, exposure to cannabinoids during critical periods of brain maturation has a profound influence on the development of GABA-ergic- (Garcia-Gil *et al.* 1999), glutamatergic- (Suarez *et al.* 2004), serotonergic- (Molina-Holgado *et al.* 1997) and the catecholaminergic system (Garcia-Gil *et al.* 1997; Fernandez-Ruiz *et al.* 2000; Hernandez *et al.* 2000). In agreement with such an impact of THC exposure early in life on the development of neurotransmitter systems, a number of papers report a dramatic effect of THC exposure in early puberty on various cognitive measures in animals (Schneider and Koch, 2003; O'Shea *et al.* 2004; Cha *et al.* 2006; Quinn *et al.* 2008).

We also noticed the relatively high symptom scores among individuals that started to use cannabis after the age of 20 years.

Quantity of weekly cannabis use

The second main finding of our study is that the amount of weekly cannabis use is equally associated with positive-, negative- and depressive symptoms (figure 2). In subjects who use cannabis excessively (>€25 per week) the odds ratio for increased negative symptoms is 3.4 (95%CI 2.9 – 4.1), for psychotic experiences the odds ratio is 3.0 (95%CI 2.4 – 3.6) and for a top 10% score on depressive symptoms the odds ratio is 2.8 (95%CI: 2.3 – 3.3). These odds ratios are similar to those reported for the association between the amount of cannabis use and developing a psychotic disorder (Moore *et al.* 2007). An association of cannabis use with depression was also found before (Patton *et al.* 2002; Moore *et al.* 2007) but not in two previous studies utilizing the CAPE (Verdoux *et al.* 2003; Stefanis *et al.* 2004).

Three previous studies reported that the association between cannabis use and psychiatric symptoms is stronger in younger subjects (Arseneault *et al.* 2002; Fergusson *et al.* 2003; Stefanis *et al.* 2004). However, the current study is the first to explicitly examine associations with specific symptom profiles. Due to the large sample size we are able to directly compare groups with different initial ages of cannabis use, including a group that started before the age of 12 years. Other strengths of the current study are the informative measure of THC exposure (€/week), use of a single well validated instrument (CAPE) in all subjects and an anonymous setting which potentially increases the questionnaire sensitivity (Buchanan and Smith, 1999; Joinson, 1999). By choosing a top10%-cape score as primary outcome, a stringent measure was selected in order to increase relevancy. Individuals with particularly high scores on self-reported psychotic

symptoms have a higher risk to develop a psychotic disorder later in life (Chapman *et al.* 1994; Poulton *et al.* 2000; Hanssen *et al.* 2005; Wiles *et al.* 2006; Yung *et al.* 2009), by choosing a top10% cut off, we intended to maximize the informational value of the study.

Web-based questionnaire

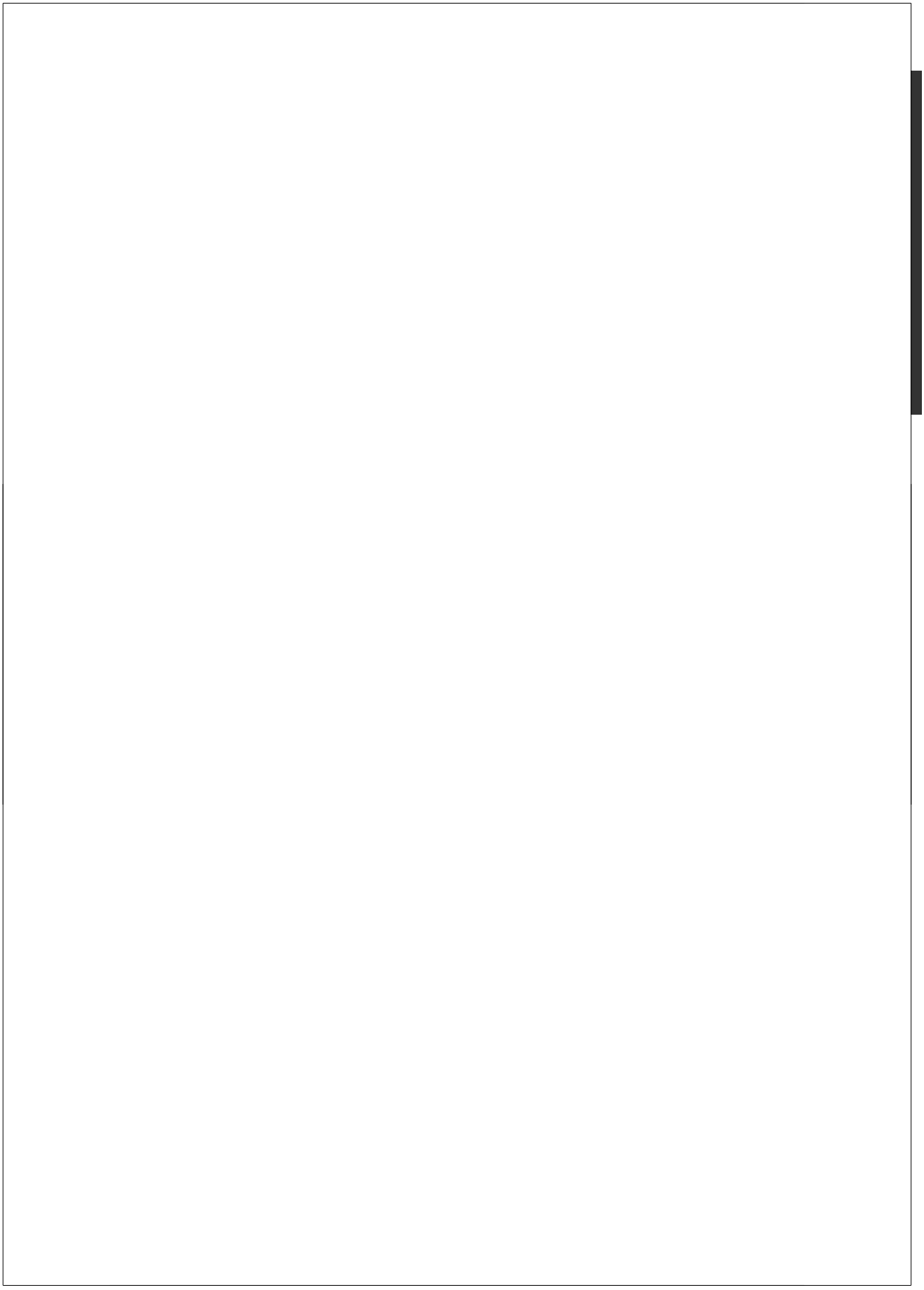
The increased availability of internet access and the development of better web-based tools have improved the possibilities to acquire information on psychiatric symptoms via the internet such that they are considered a valid additional method in epidemiological research (Meyerson and Tryon, 2003; Gosling *et al.* 2004; Balter *et al.* 2005; Ekman *et al.* 2006). Over the last years, numerous internet based assessments have been validated that measure a variety of psychiatric phenotypes ranging from cannabis abuse to depression (Houston *et al.* 2001; Graham *et al.* 2006; Coles *et al.* 2007; Lin *et al.* 2007; Vallejo *et al.* 2007; Cuijpers *et al.* 2008; Graham and Papandonatos, 2008; Khazaal *et al.* 2008; Spek *et al.* 2008; Donker *et al.* 2009). On a more critical note the use of web-based assessments could potentially have lead to instrument inaccuracy or to information bias. However, the distribution of this potential inaccuracy is most likely independent of cannabis use (exposure measure), and psychiatric experiences (outcome measure) and is therefore unlikely to have systematically influenced the reported associations. A second potential concern is the possibility of selection bias due to the online subject recruiting strategy. However, as described in the sensitivity analysis our results are fairly robust against selection bias. Even in the unlikely event that selection has lead to a 20 percent increase in participants with early cannabis use and high symptoms score the results would remain significant.

A potential limitation is the limited availability of information on concomitant drug use. However, analysis of these data shows that after adjusting for concomitant drug use, the odds ratio for psychotic experiences increased to 14.4 (95%CI 3.3 – 61.6) in the group that started before the age of 12 years. Therefore, these adjusted odds ratios do not weaken the associations reported earlier.

Finally, it is important to notice that the association presented here are based on current (last month) and not cumulative cannabis use. It is not known what proportion of users have a longer history of cannabis use, implicating that we cannot disentangle acute intoxication from long term effects.

Despite the fact that the informational value of the current dataset is limited by the retrospective and cross sectional design precluding any inference on causality, this study shows that heavy current cannabis use is associated with a different symptom profile than early cannabis use. This finding converges with epidemiological and animal studies and

supports the hypothesis that there is a window of increased vulnerability of the maturing brain to the effects of exo cannabinoids such as THC, during early puberty. Given the developmental nature of psychotic disorders (van and Kapur, 2009) further studies are warranted to examine the influence of cannabis on brain development.



6

Cigarette smoking and cannabis use are equally strongly associated with psychotic-like experiences

a cross-sectional study in 1,929 young adults

W.A. van Gastel[1]

J.H. MacCabe[2]

C.D. Schubart[1]

A. Vreeker[1]

W. Tempelaar[1]

R.S. Kahn[1]

M.P.M. Boks[1]

Psychological Medicine (2013) **18**, 1-9

1. Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Department of Psychiatry, HP. A01.468, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands

2. Department of Psychosis Studies, Institute of Psychiatry, King's College London, UK

ABSTRACT

Background

Cannabis use is associated with increased risk for psychotic-like experiences (PLE) and psychotic disorders. It remains unclear whether this relationship is causal or due to confounding.

Methods

1,929 young adults aged 18-30 years participated in a nationwide internet-based survey in the Netherlands and gave information on demographics, substance use, parental psychiatric illness and filled out the Community Assessment of Psychic Experiences (CAPE).

Results

Cigarette smoking and cannabis use were equally strongly associated with frequency of PLE (β=0.098 and 0.079, respectively, $p<0.05$). Cannabis use was associated with distress from PLE in a model adjusted for an elaborate set of confounders excluding smoking (β=0.082, $p<0.05$). However, when cigarette smoking was included in the model, cannabis use was no significant predictor of distress from psychotic-like experiences. Cigarette smoking remained associated with distress from PLE in a fully adjusted model (β=0.107, $p<0.001$)

Conclusion

Smoking is an equally strong independent predictor of frequency of PLE as monthly cannabis use. These results suggest that the association between moderate cannabis use and psychotic-like experiences is confounded by cigarette smoking.

INTRODUCTION

Cannabis use has been implicated as a risk factor for psychotic symptoms, ranging from subclinical psychotic-like experiences (PLE) to clinically defined schizophrenia (Andreasson *et al.* 1987; Arseneault *et al.* 2002; van Os *et al.* 2002; Fergusson *et al.* 2003; Henquet *et al.* 2005; Moore *et al.* 2007; Schubart *et al.* 2010; van Gastel *et al.* 2012). There is evidence of a dose-response effect: heavy and long-term cannabis use and an initiation of use before the age of 16 are associated with an elevated rate of PLE (Arseneault *et al.* 2002; Monshouwer *et al.* 2006; Schubart *et al.* 2010; van Gastel *et al.* 2012). Moreover, the onset of psychosis is earlier in cannabis-using patients (Large *et al.* 2011) and cannabis use may exacerbate symptoms in patients with established psychosis (Mullin *et al.* 2012).

Although firmly established, the nature of the association between cannabis use and psychotic symptoms remains subject to debate (Murray *et al.* 2007). Several underlying mechanisms have been proposed such as the persistence of normally transient cannabis-induced psychotic symptoms (Cougnard *et al.* 2007), an adverse impact on the developing endo-cannabinoid and/or dopaminergic system (Caspi *et al.* 2005; Henquet *et al.* 2006; Bossong and Niesink, 2010; Costas *et al.* 2011) and reverse causality, whereby individuals with PLE are more likely to start using cannabis in an attempt to 'self-medicate' their distress (Henquet *et al.* 2005; Macleod *et al.* 2007). A further possibility is that the association between cannabis consumption and psychotic symptoms could arise through confounding (Macleod and Hickman, 2006; Macleod *et al.* 2007; van Gastel *et al.* 2012). A substantial overlap exists between risk factors for cannabis use and mental health problems in young adolescents (van Gastel *et al.* 2012), and in many studies, the association between cannabis use and mental health problems is diminished following adjustment for confounders (e.g. (Monshouwer *et al.* 2006) (Macleod *et al.* 2004; van Gastel *et al.* 2012)).

Tobacco smoking may be such a confounder. Nicotine dependency is associated with psychotic symptoms: several longitudinal studies found a dose-response relationship between cigarette smoking in adolescence and later psychotic symptoms in the general population (Degenhardt and Hall, 2001; Weiser *et al.* 2004; Wiles *et al.* 2006; Sorensen *et al.* 2011) and the majority (70-85%) of patients with schizophrenia smokes cigarettes (Lasser *et al.* 2000; Ziedonis *et al.* 2008). Furthermore, cannabis use and cigarette smoking are strongly correlated (Agrawal *et al.* 2012) and in most European countries, cannabis is usually consumed in combination with tobacco. Thus, the question arises to what extent the relationship between cannabis use and PLE is influenced by cigarette smoking. In a large cross-sectional sample, we address this issue by comparing two elaborately

adjusted models of the association between cannabis use and frequency of psychotic-like experiences and associated distress, both with and without adjustment for cigarette smoking.

METHODS

Participants

The data were collected in the Netherlands over the period of August 2006 until April 2011 using a research website designed for this purpose. Participants were recruited via advertisements on websites, chat clients, college intranet sites, during college introduction periods and in 'coffeeshops' (licensed retailers of cannabis products). As an incentive, participants had a chance of winning a prize, ranging from a Hawaiian garland and credit for online shopping to a parachute-jump or a laptop computer. Web-based questionnaires covered socio-demographic characteristics, lifestyle, social environment and psychosocial functioning. In order to detect random answering and automated answers by internet robots, verification items were included. All participants gave online informed consent and the study was approved by the ethics committee of the University Medical Center Utrecht.

Measurements

Psychotic-like experiences

The Community Assessment of Psychic Experiences (CAPE) was used to assess lifetime PLE (Stefanis *et al.* 2002; Konings *et al.* 2006). The CAPE has discriminative validity in community samples (Stefanis *et al.* 2002; Konings *et al.* 2006). Each item measures the frequency and associated distress of psychotic experiences, each rated on a four-point scale ranging from 'never'/'not distressed' (1) to 'nearly always'/'very distressed' (4). If the frequency was 'never', distress was not inquired and automatically set to zero. The scores were rescaled by subtracting the minimum score (as suggested for the PANSS instrument by Obermeier and colleagues (Obermeier *et al.* 2010) such that a person reporting no psychotic symptoms scored zero. Scores on the Frequency and Distress scales were used as outcome measures and a post-hoc analysis was performed on the Positive, Negative and Depressive subscales.

Cannabis use

Cannabis use was measured by asking 'how often do you use cannabis?'. Individuals who reported cannabis use on at least a monthly basis were classified as cannabis users; use of cannabis at least weekly was coded as heavy use. Subjects were also asked at what age they started using cannabis.

Cigarette smoking
Cigarette smoking was defined as daily smoking for at least one month during the past year.

Other covariates
Heavy alcohol use was defined as more than 21 drinks per week for men and more than 14 for women, according to the Dutch directive for alcohol consumption(de Beer and van de Glind, 2009b). Lifetime use of any other illicit substances was recorded. Nationality was based on the country of birth of the grandparents; subjects with two or more grandparents born outside the Netherlands were defined as non-native. Education was coded according to the three educational tracks in Dutch secondary schools and higher education: vocational, polytechnic and scientific education. Treatment of one or both parents for a mental disorder, including addiction, psychotic and affective symptoms, was also included.

Data analysis
All analyses were carried out with the statistical package for the social sciences (SPSS 20.0). Listwise exclusion was applied for missing values. Linear regressions were carried out, with the CAPE Frequency and Distress scores as outcome measure after verification of statistical assumptions using scatterplots of the residuals. The association between cannabis use and CAPE Frequency and Distress was assessed, firstly in a crude model and secondly in a model adjusting for confounders age and gender, plus other potential confounders that were associated with cannabis use and the outcome measures at $p<0.05$. Thirdly, cigarette smoking was added to both crude and fully adjusted models. The interaction between cannabis use and smoking was also investigated. Lastly, post-hoc analyses were performed with the Positive, Negative and Depressive subscales as outcome measures, and the effect of frequency of cannabis use was explored.

RESULTS

There were 27 missing values for ethnicity, 22 for mental disorder of parents and 8 for educational track. Listwise exclusion of these resulted in a sample of 1,929 adolescents aged 18-30 years, 947 (49.1%) male. Table 1 lists sample characteristics, stratified by monthly cannabis use: *non-users* used cannabis never or infrequently, *users* consumed cannabis at least monthly. Groups differed significantly on all characteristics. About one-third of the total sample (36.5%) had never used cannabis, another 9.3% less than yearly. Among cannabis users, 50.3% started using between the age of 15 and 17 years; 30.3% of them started using before the age of 15. The proportion of daily cigarette smokers was 39% overall, and was 70.9% among cannabis users.

Table 1. Sample characteristics of total study sample (n=1929), stratified by cannabis use

Characteristic	total (n=1929)	non-users (n=1000)	users (n=929)	X^2 or t	p-value
Age in years (mean, sd)	21.6 (2.6)	21.2 (2.3)	22.0 (2.8)	-6.345	<0.001
Male gender (n, %)	947 (49.1%)	378 (37.8%)	569 (61.2%)	106.0	<0.001
≥2 grandparents born outside Netherlands (n, %)	290 (15.0%)	87 (8.7%)	203 (21.9%)	65.2	<0.001
Low level of education (n, %)	585 (30.3%)	198 (19.8%)	387 (41.7%)	108.9	<0.001
Parent(s) treated for mental health problem (n, %)	493 (25.6%)	198 (19.8%)	295 (31.8%)	36.2	<0.001
Cigarette smoking (n, %)	762 (39.5%)	103 (10.3%)	659 (70.9%)	741	<0.001
Regular alcohol consumption (n, %)	1656 (85.8%)	810 (81.0%)	846 (91.1%)	40.2	<0.001
Other Illicit substance use ever (n, %)	707 (36.7%)	59 (5.9%)	648 (69.8%)	845.7	<0.001

Association between cannabis use and PLEs

The regression coefficients (β) and p values for the association between cannabis use and psychotic experiences, as measured by the CAPE Frequency and Distress scores, are shown in Table 2. The results show that cannabis use was related to the CAPE Frequency and Distress scores, even when an elaborate set of confounders was taken into account (β=0.123, p<0.001; β=0.082, p<0.05, respectively).

Association between cannabis use, smoking and PLEs

The association between cannabis use, smoking and frequency of PLE, as measured by the CAPE, is shown in Table 2. Both cannabis use and smoking were associated with frequency of PLE, in a crude (β=0.110; β=0.128, respectively, p<0.001) as well as a fully adjusted model (β=0.079, p<0.05; β=0.098, p<0.01, respectively). No significant interaction effects were found for cannabis and smoking, although we had limited power to find such an effect.

Association between cannabis use, smoking and distress from PLEs

The association between cannabis use, smoking and distress from PLE, as measured by the CAPE, is shown in Table 2. Cigarette smoking was significantly associated with distress from PLE, both in a crude (β=0.132, p<0.001) and a fully adjusted model (β=0.107, p<0.001). cannabis use was not significantly associated with distress from PLE when

cigarette smoking was included as a covariate, in a crude nor an fully adjusted model. Again, no significant interaction effects were found for cannabis and smoking, although we had limited power to find such an effect.

Association between cannabis use, smoking and CAPE positive, negative and depressive subscales

Cannabis use and smoking were significantly associated with the score on the CAPE Positive subscale, in a crude (β=0.135, $p<0.001$; β=0.107, $p<0.001$, respectively) and an adjusted model (β=0.117, $p<0.001$; β=0.082, $p<0.01$, respectively). For the score on the CAPE Negative subscale, the association with cannabis use was only significant in a crude model alongside smoking (β=0.102, $p<0.001$), whereas smoking remained significantly associated in a fully adjusted model (β=0.096, $p<0.01$ crude and β=0.080, $p<0.01$ adjusted). cannabis use was only associated with the score on CAPE Depressive subscale in a crude model without smoking (β=0.088, $p<0.001$); smoking remained significantly associated adjusted model (β=0.129, $p<0.001$ crude and β=0.086, $p<0.01$ adjusted).

Frequency of cannabis use

For heavy cannabis use, the association pattern with frequency of PLE was the same as for monthly cannabis use: both cannabis use and smoking were associated with frequency of PLE, in a crude (β=0.124; β=0.122, respectively, $p<0.001$) as well as a fully adjusted model (β=0.100; β=0.093, respectively, $p<0.01$). However, heavy cannabis use was only associated with distress from PLE in a crude model (β=0.055, $p<0.05$) but not in the adjusted model. Smoking remained associated with distress from PLE alongside heavy cannabis use (β=0.125, $p<0.001$ crude, β=0.100, $p<0.01$ adjusted).

DISCUSSION

In a large sample of young adults aged 18 to 30 years old, we found that cigarette smoking was as strongly associated as cannabis use with frequency of psychotic-like experiences (PLE), and even more strongly with distress from PLE. Where cigarette and cannabis smoking were included in the same model, cigarette, but not cannabis smoking, was associated with distress from psychotic symptoms. This suggests that the relationship between cannabis use and distress from PLE is confounded by cigarette smoking. Weekly cannabis use however, was associated with distress from PLE alongside cigarette smoking in a crude model, suggesting that at higher frequencies of cannabis use the confounding by cigarette smoking is less pronounced.

Cigarette smoking and psychotic-like experiences

The associations we found for cigarette smoking echo previous studies. Degenhardt and

colleagues found that both cannabis use and cigarette smoking are associated with a range of mental health problems, including psychosis (Degenhardt and Hall, 2001). Saha and colleagues (Saha *et al.* 2011) showed that individuals who smoke cigarettes were more likely to endorse delusional-like experiences, as were those who had been diagnosed with cannabis dependence or those who had started cannabis use before the age of 16 years. In parallel with our findings, they also showed that the association between daily smoking and delusional-like-experiences persisted after adjustment for other risk factors, whereas the association with cannabis use dependence did not.

The association between cigarette smoking and PLE can be explained in several ways. First of all, cigarette smoking could increase the risk for PLE via a biological mechanism. In support of this, Brody and colleagues (Brody *et al.* 2004) showed that smoking causes acute dopamine release in the ventral striatum and nicotinergic cholinergic neurotransmission was reported to be related to schizophrenia (Dean *et al.* 2003; Ripoll *et al.* 2004).

A second possibility is that nicotine is taken in an attempt to alleviate psychotic-like symptoms. There is some evidence that nicotine may alleviate symptoms associated with psychotic disorders (Punnoose and Belgamwar, 2006) as it improves negative symptoms in psychotic patients and cognitive functioning in both healthy subjects and in psychotic patients (Dalack *et al.* 1998; Lyon, 1999; Barr *et al.* 2008; Jubelt *et al.* 2008; Wignall and de Wit, 2011). On the other hand, research in patients with schizophrenia has shown an association between nicotine dependence and worse psychotic symptoms (Kelly and McCreadie, 1999; Krishnadas *et al.* 2012). A third (slightly more remote) possibility is that PLE result from nicotine withdrawal effects, as this has been observed in cases of psychotic patients (Dalack and Meador-Woodruff, 1996).

A fourth possibility is that the association between cigarette smoking and PLE could be due to confounding by one or more other factors. In other words: individuals who are prone to PLE are also prone to smoke cigarettes. Psychosocial stress increases the risk of PLE and stress reduction is a frequent reason to smoke (Mobascher and Winterer, 2008; Compton *et al.* 2009). This explanation is supported by our finding of a strong association between cigarette smoking and distress associated with PLE.

Cannabis use and psychotic-like experiences

Cannabis use has received much attention as a potential cause of PLE and psychotic disorders (Macleod *et al.* 2004; Moore *et al.* 2007). Regarding the association between moderate cannabis use and frequency of PLE, our findings are equivocal. Cannabis use was associated with frequency scores, also in a fully adjusted model. This shows that cannabis use is independently associated with frequency of PLE and a causal relationship is a possibility. However, our finding that monthly cannabis use and cigarette smoking

Table 2. Standardized regression coefficients (β) and p-values for the association between monthly cannabis use, daily smoking and CAPE-scores for crude and adjusted models. For the adjusted models, associations between all factors and CAPE-scores are also displayed. βs with a p-value below 0.05 are shown in italic.

	Model	Predictor	Frequency	Distress
Monthly cannabis use	**Crude**	**Cannabis use**	*0.190 (<0.001)*	*0.132 (<0.001)*
	Adjusted	**Cannabis use**	*0.123 (<0.001)*	*0.082 (0.008)*
		Age	-0.033 (0.133)	-0.030 (0.186)
		Male gender	-0.048 (0.034)	*-0.078 (<0.001)*
		Foreign ethnicity	*0.088 (<0.001)*	*0.072 (0.002)*
		Low education	*0.062 (0.006)*	0.033 (0.148)
		Heavy alcohol use	-0.006 (0.793)	-0.017 (0.463)
		Other Illicit substances (ever)	0.050 (0.093)	0.056 (0.063)
		Parent(s) treated for mental problem	*0.144 (<0.001)*	*0.141 (<0.001)*
Monthly cannabis use and daily smoking	**Crude**	**Cannabis use**	*0.110 (<0.001)*	0.050 (0.082)
		Smoking	*0.128 (<0.001)*	*0.132 (<0.001)*
	Adjusted	**Cannabis use**	*0.079 (0.017)*	0.034 (0.310)
		Smoking	*0.098 (0.001)*	*0.107 (<0.001)*
		Age	-0.036 (0.109)	-0.032 (0.152)
		Male gender	-0.044 (0.054)	*-0.082 (<0.001)*
		Foreign ethnicity	*0.089 (<0.001)*	*0.072 (0.001)*
		Low education	*0.048 (0.039)*	0.017 (0.453)
		Heavy alcohol use	-0.010 (0.644)	-0.022 (0.342)
		Other Illicit substances (ever)	0.030 (0.316)	0.034 (0.260)
		Parent(s) treated for mental problem	*0.139 (<0.001)*	*0.136 (<0.001*)

were equally strongly associated with frequency scores argues against a specific causative effect of moderate cannabis use on PLE. Although it remains possible that nicotine and cannabis are causally related to PLE, the non-specificity of the associations does suggest that reverse causation or confounding are at play.

Also regarding distress from PLE, our findings are not supportive of the view of cannabis use as a cause of psychotic experiences. If cannabis were to cause highly distressing PLE, the association would persist even after complete adjustment for confounding. But even with inevitable residual confounding at play, monthly cannabis use was not significantly associated with distress from PLE when combined with smoking in crude and adjusted models. This implies that the association between highly distressing PLE and cannabis use is confounded by cigarette smoking, and possibly other confounders.

Overall, our findings fit the hypothesis that individuals who are prone to PLE, particularly if associated with high distress, are more inclined to use cannabis. If this is the case, moderate cannabis use, as cigarette smoking, could be viewed as a mere indicator of risk for PLE, and thus mental health problems in general (Johns and van Os, 2001; Yung *et al.* 2003; Hanssen *et al.* 2005) instead of a causative factor. This view is consistent with the accumulation of risk factors in the group of subjects using cannabis at least monthly, including foreign ethnicity (van Gastel *et al.* 2012), low educational level (Ruhrmann *et al.* 2010) and family history of a mental disorder (Mortensen *et al.* 1999; Mattejat and Remschmidt, 2008).

In contrast to monthly cannabis use, the association between weekly cannabis use and distress from PLE did persist alongside cigarette smoking in a crude model. This shows that frequency of use might play a key role in the mechanism underlying the association and that a causal relationship between cannabis use and PLE may exist for higher frequencies of use. Our findings are consistent with a model whereby the tendency to use cannabis is associated with increased levels of psychotic like experiences, and early or heavy use of cannabis leads to additionally increased psychosis proneness.

Limitations

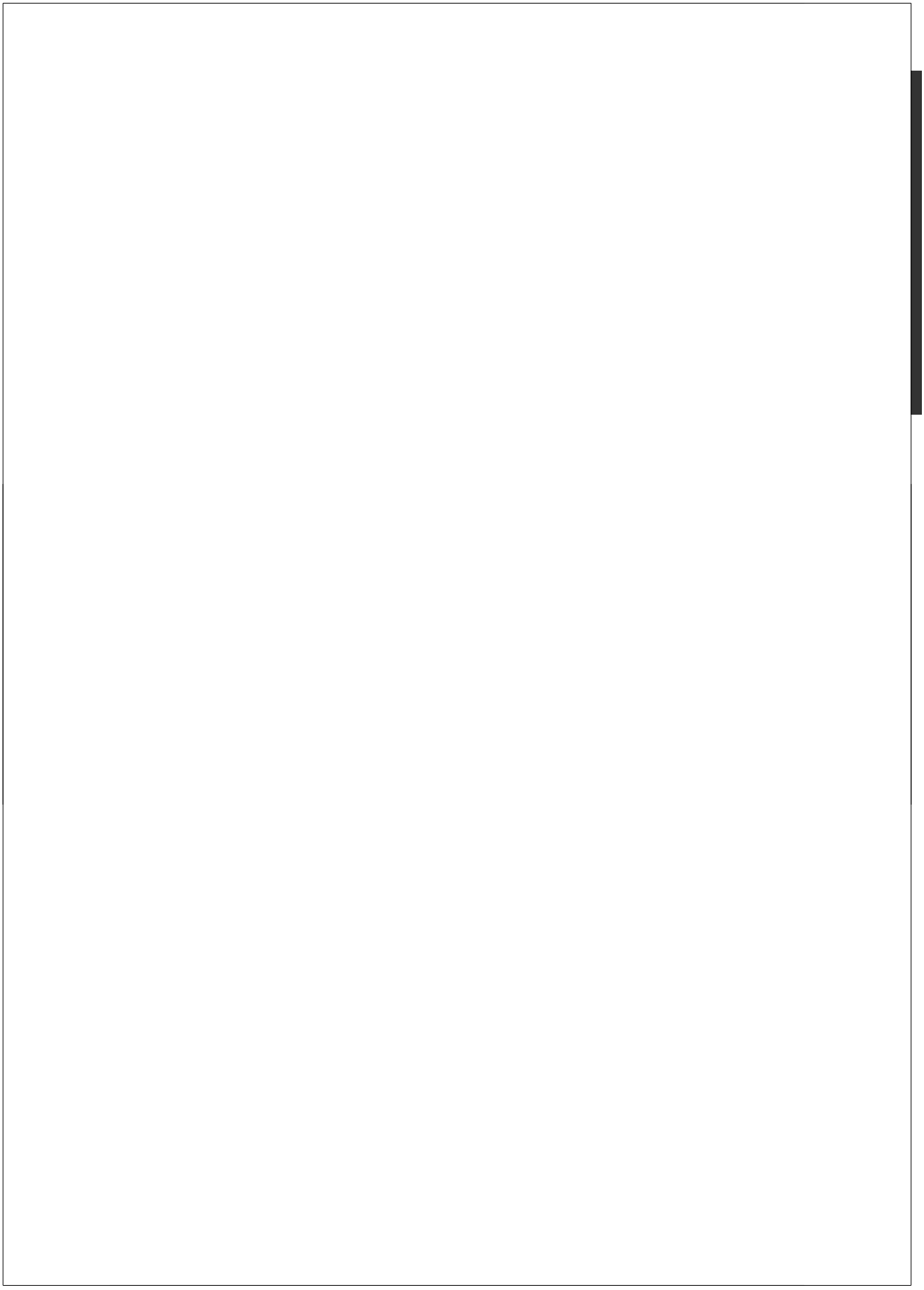
A major limitation is that the study is cross-sectional, precluding firm conclusions regarding causality. Nonetheless the results are in line with longitudinal studies linking both cannabis use (Arseneault *et al.* 2002; van Os *et al.* 2002; Henquet *et al.* 2005; Rossler *et al.* 2012) and cigarette smoking to (subclinical) psychotic symptoms (Degenhardt and Hall, 2001; Weiser *et al.* 2004; Wiles *et al.* 2006; Sorensen *et al.* 2011). Furthermore, our data were gathered by self-report via the internet, possibly leading to either over- or underreporting of undesirable behaviour such as cannabis use. However, studies comparing psychometric

and biometric measures of cannabis use (among which urine and hair-tests) show good reliability of self-report measures (Ledgerwood *et al.* 2008; Zaldivar *et al.* 2009). Although recent studies have shown that the internet is a suitable instrument for scientific research (Meyerson and Tryon, 2003; Gosling *et al.* 2004; Balter *et al.* 2005; Ekman *et al.* 2006; Vleeschouwer *et al.* 2012) and potential bias is unlikely to be systematic, we cannot rule out that our sample is in some way not representative of the general population.
The CAPE questionnaire inquires after lifetime psychotic experiences and these may be hard to distinguish from acute intoxication effects of cannabis. There is however some evidence that high CAPE scores associated with acute cannabis intoxication are a reflection of psychosis proneness as well (GROUP researchers, 2011). Likewise, the time of the last cigarette the day of participation was not assessed.

As in other studies, there was a large overlap between smoking and cannabis use in our sample (Lynskey *et al.* 1998; Degenhardt and Hall, 2001). Even so, nearly a third of cannabis users in this study were non-smokers of cigarettes, the large sample size allows us to tease out the relative importance of these risk factors, and the consistency of the findings in unadjusted and adjusted models suggests that these findings are stable.

Finally, unknown sources of confounding may remain: although measures of demographic factors and substance use were available, residual confounding by extensive behavioural and psychopathological factors such as attention-deficit hyperactivity disorder, externalising behaviour and conduct disorder (Monshouwer *et al.* 2006; Karatekin *et al.* 2010; Lee *et al.* 2011; Malcolm *et al.* 2011) cannot be ruled out. Factors that may play a role, but that were not measured, are age at onset of cigarette smoking (Saha *et al.* 2011), urbanicity, socio-economic status, social support and household composition (van Gastel *et al.* 2012).

Despite its limitations, the present study is an important addition with the existing literature, since it demonstrates that smoking is equally strongly associated to PLE as cannabis use. Moreover, the association between monthly cannabis use and distress from PLE is strongly influenced by cigarette smoking. Our findings are consistent with a model whereby individuals that are prone to PLE are more inclined to smoke cigarettes and use cannabis, and whereby early or heavy use of cannabis leads to additionally increased psychosis proneness.



7 Summary and general discussion

Cannabis use has been implicated as a risk factor for mental health problems, and (subclinical) psychotic symptoms in particular. This thesis aimed to provide the debate revolving around this theme with scientific arguments. Here, a short summary of the results of the studies is given, as well as methodological considerations, implications for clinical practice and health policy and a general conclusion is drawn.

CANNABIS USE AND MENTAL HEALTH PROBLEMS

In **Chapter 2** cannabis use and mental health problems in a large secondary school sample of Utrecht province was studied, in collaboration with the Public Health Center of the region. The aim of this study was twofold: first, to investigate the association between cannabis use and mental health problems and second, to assess the direct association of cannabis use itself with other risk factors associated with mental health problems in this sample. Interestingly, while cannabis use was associated with a fourfold risk of mental health problems in a crude model, there was no dose-response association and there was no association present when other risk factors were taken into account. Furthermore, there was a large overlap between risk factors for cannabis use and for poor mental health. This indicates that the relationship between cannabis use and mental health was confounded by other risk factors in this study.

Chapter 4 addressed the association between cannabis use and mental health problems in young adults. As in chapter 2, the effect of other risk factors for poor mental health was taken into account. In this study, the association between cannabis use and mental health *did* remain significant in a fully adjusted model, suggesting an independent association between cannabis use and mental health problems. However, in this study we were not able to correct for such an elaborate set of other risk factors. This makes residual confounding likely, in which case the association between cannabis use and mental health problems appears larger than it really is because the contribution of unknown other factors ('third factors') to poor mental health is unjustly attributed to cannabis. This study specifically investigated the age at onset of cannabis use and the frequency of use. Weekly cannabis use was found to have a slightly stronger relationship with mental health problems than monthly cannabis use, and both of these relationships were independent of the age at onset of use. This indicates that whatever mechanism is at play, it is not entirely due to an enduring effect of early brain damage resulting from cannabis use during a critical phase of brain development. Furthermore, this study showed that women who use cannabis are at a higher risk for mental health problems than male cannabis users.

In both studies on the association between cannabis use and general mental health it is argued that irrespective of the causal nature of the association, cannabis use can be seen as an indicator of risk for mental health problems.

CANNABIS USE AND PSYCHOTIC-LIKE EXPERIENCES

Chapter 3 described a nationwide sample of young adolescents, surveyed for the Health and Behaviour in School-aged Children study of the World Health Organisation. This study was conducted in collaboration with the Department of Interdisciplinary Social Sciences in Utrecht and found that young adolescents who use cannabis report more positive psychotic-like experiences. This dose-response relationship was independent of other risk factors. One of the user groups in this study comprised young adolescents who had used cannabis in the past, but who had abstained from this for at least one year. This group did not report fewer positive psychotic-like experiences than did the group that used cannabis heavily at the time of the survey. This finding is consistent with the hypothesis that early cannabis use might lead to an enduring adverse impact on the developing brain, expressed as a specific vulnerability for psychosis, but may also be explained by accumulating risk factors in this group.

Chapter 5 distinguished two properties of cannabis use; age at onset (measured retrospectively) and intensity of use. The latter was measured by means of the amount spent on the consumed cannabis product, since market value and THC-concentration are correlated in the Netherlands (van Laar, 2010). The results showed that an early age at onset was associated with positive and negative psychotic-like experiences. Compared to participants who had started to use cannabis between the age of 15 and 18 years, which was the most common age at onset, participants who had started to use before the age of 12 years had a threefold chance of current positive psychotic experiences. Considering intensity of use, a dose-response relationship was found for all three symptom dimensions of psychotic-like experiences that were measured; positive, negative and depressive. Participants in the highest user category, the equivalent of roughly seven weed-joints a week or more, had a threefold risk of psychotic-like experiences. For cannabis users in the second highest user category, the equivalent of roughly three to seven weed-joints a week, this risk was nearly twofold.

Chapter 6 was designed to investigate whether the association between cannabis use and psychotic-like experiences is influenced by cigarette smoking. Cigarette smoking was found to be an equally strong predictor of psychotic-like experience as cannabis use and an even better predictor of distress associated with these experiences. Since high

distress associated with psychotic-like experiences is thought to predict transition to clinical psychosis, this association is clinically very relevant. These results suggest that the association between moderate cannabis use and psychotic-like experiences is strongly influenced by cigarette smoking and that individuals prone to psychotic-like experiences are more inclined to smoke cigarettes and use cannabis. The strong and independent association between psychotic-like experiences and heavy cannabis use however, shows that frequency of use might play a key role in the mechanism underlying the association and that a causal relationship may exist for higher doses.

Taken together, the results of studies in this thesis investigating psychotic-like experiences implicate that the association with moderate cannabis use is more likely to be the result of pre-existing vulnerability, in the form of either psychosis-proneness or the burden of environmental risk factors, both leading to cannabis use. However, early and heavy use do appear to causally increase the risk of psychotic-like experiences.

METHODOLOGICAL CONSIDERATIONS

The most important limitation of the studies in this thesis is that they are of a cross-sectional nature, with measurements conducted at one point in time. Therefore, firm conclusions regarding causality cannot be drawn. Nonetheless the results are in line with longitudinal studies linking cannabis use to a variety of mental health problems, including (subclinical) psychotic symptoms (Arseneault *et al.* 2002; Fergusson *et al.* 2002; van Os *et al.* 2002; Degenhardt *et al.* 2003; Henquet *et al.* 2005; Moore *et al.* 2007; Rossler *et al.* 2012). Furthermore, the design of several of the studies do leave room to investigate the likelihood of a causal relationship; for example by assessing the robustness of the effect against an extensive correction for other risk factors.

Sampling

The samples described in this thesis may not be representative for the general population. For the chapters on adolescents (chapter 2 & 3), school surveys were used. Respectively 71% and 47% of invited schools participated in the study. For chapter 3, the study with the lowest response rate, there was no selective drop-out in terms of urbanicity and school size. Selection bias could also have occurred at class-level, missing out truants and those who often miss school due to illness. However, since truancy is positively associated to substance use and mental health problems, this bias is more likely to have led to an underestimation of the effect.

The chapters studying young adults (chaper 4,5 & 6) applied the research website CannabisQuest.nl. Sampling from universities and coffee shops may have resulted in a sample enriched for students and cannabis users. The study in chapter 5 conducted an analysis for sensitivity to selection bias. The impact of a decrease in the number of participants with a high total score on the main dependent variable (CAPE-score) and either one of the major predictors (early or heavy cannabis use) on the found effect sizes was calculated. This showed that the results were fairly robust to the effects of sampling bias. Even in the unlikely event that selection bias led to a 20% or 63% increase in cases, respectively, the results would have remained significant. Furthermore, for all research in this thesis potential sampling bias is unlikely to be systematic. Still, despite this and our efforts to minimize the chance of sampling bias, we cannot rule out that the samples were in some way not representative of the general population.

Internet-based data acquisition

For the data-acquisition of chapter 4, 5 and 6, the internet was used as an instrument. Although online questionnaires are now considered a valuable additional method in epidemiology (Meyerson and Tryon, 2003; Gosling *et al.* 2004; Balter *et al.* 2005; Ekman *et al.* 2006), their use also provokes critical scrutiny. All studies in this thesis using the internet as an instrument applied verification items, and casewise exclusion was applied when these were not answered correctly. This way, automated answers by 'internet bots' were filtered out, as well as data of unmotivated participants not putting effort into it. In order to assess the validity of the most important online tool we applied, the CAPE questionnaire, our group performed analyses on cross-validity of our own online and pen-and-paper versions of this questionnaire (Vleeschouwer *et al.* 2012). This study showed that although measurement invariance (i.e. no difference in score due to assessment method) could not be fully supported, the small effect sizes indicate that the online CAPE questionnaire is a valid tool for research. It also showed that the online version is somewhat stricter, in the sense that a person with high psychosis proneness would have a lower score on the online version than on the pen-and-paper version. Herefore, the application of the online CAPE questionnaire is unlikely to have led to an overestimation of the associations described in this thesis.

Another potential disadvantage of online surveys is that participants cannot be screened for intoxication; the acute effects of cannabis might therefore have influenced the scores of the questionnaire. Particularly, the CAPE questionnaire inquires after lifetime psychotic experiences and these may be hard to distinguish from acute intoxication effects of cannabis. There is however evidence that high CAPE scores associated with acute cannabis intoxication are a reflection of psychosis proneness as well (GROUP researchers, 2011).

Self-report

All data used in this thesis were gathered by self-report. Potentially, this leads to either over- or underreporting of undesirable behaviour such as cannabis use. However, studies comparing psychometric and biometric measures of cannabis use (among which urine and hair-tests) show good reliability of self-report measures (Ledgerwood *et al.* 2008; Zaldivar *et al.* 2009). The data for chapter 2 and 3 were collected via school surveys. By administering the questionnaires in school classes and by assuring anonymity, validity and reliability are assumed to improve (Smit *et al.* 2002).

Measures of cannabis use

In the field of cannabis use and mental health research, there is no real consensus on the best measure of cannabis use. Various measure of exposure help shed light on the nature of the association; an early age at onset for example fits best with a causal explanation, while frequency of use is a-specific. Measures of cannabis used in this thesis are: an early age at onset, frequency of use and expenditure on consumed cannabis. The latter was chosen since in the Netherlands, the price of cannabis products is correlated with its THC-contents (van Laar, 2011). Other measures of cannabis that could be used are total lifetime consumption, type and consumption method of cannabis (since THC-levels vary per type) and an exact mapping of the pattern of use since first onset. Ideally, this could be correlated to the pattern of mental health problems over the same period. Of consideration is the timespan covered by the dependent measure, which should preferably correspond to the measured timespan of cannabis use. For example, the CAPE questionnaire covers lifetime psychotic-like experiences and a predictive model is served best by a lifetime measure of cannabis use. Of course, self-report on a sensitive issue as drug use, should be approached with extra scrutiny.

Of importance is the distinction between cut-off scores for cannabis use (as applied in chapter 2, 4 and 6) and user groups (used in chapter 3 and 5). When cut-off scores are used, the interpretation of the results should take into account that the group of 'monthly cannabis use' actually covers 'at least monthly', so also weekly and daily users. This carries the risk for inflation of the effect for subjects at the lower end of this range.

Residual confounding

Since statistical procedures for correcting for confounders are not infallible and unknown sources of confounding may remain, residual confounding cannot be ruled out. Although the studies in this thesis statistically accounted for elaborate sets of other risk factors, residual confounding by extensive behavioural and psychopathological factors could have occurred. Such residual confounding may be caused by for example urbanicity, intelligence, physical disabilities, life stressors and traumatic experiences.

Future research on the association between cannabis use and mental health would gain in generalizability by applying as many different measures of cannabis use as possible. These include age at onset, accumulated lifetime use, course of cannabis use over time and preferred type. Furthermore, self-report measures should be backed up by biometric measures of THC-concentration in blood, urine and/or hair. Especially longitudinal designs should incorporate this extensive typography of cannabis consumption, since course of cannabis use could then be compared to course of symptoms and synchronicity of change could be investigated. In addition, these studies would profit from including other risk factors for mental health problems in the design. These should at least include: urbanicity, use of other illicit substances, education level and intelligence, socio-economic status, familial psychiatric liability, traumatic experiences, personality factors as well as an extensive assessment of mental health. Furthermore, the possibly antipsychotic properties of CBD deserve more attention, especially with regards to whether it would be a good addition to or even replacement for known antipsychotics.

Genetic mediation for the association between cannabis use and mental health remains a viable research option; recent findings by our group show that the PPFIA1 gene, coding for Liprin-alpha-1 (a protein) may well identify individuals at increased risk for mental health problems when they use cannabis.

Until now, research has mainly focussed on the association between cannabis use and mental health itself. Research in this field is ethically bound to observational studies and this type of research does not easily allow for causal inference. A good and pragmatic way to provide a scientific basis for effective policies would be to refocus on the health- and social effects of policies regulating the use of cannabis (Werb *et al.* 2010) and on defining and testing risk profiles for vulnerable cannabis users (Fischer *et al.* 2009).

The research in this thesis could help narrow the gap between fundamental and applied research in this field, because it provided a set of risk factors that could be combined into such a risk profile. Especially female gender, a young age at onset, heavy use, familial psychiatric vulnerability and hard drug use at young age (even once) were found to increase the risk of psychiatric problems. Factors that should also be included in a risk profile for young adolescents, are regular truancy and absence, being bullied, not enjoying school or perceiving it as unsafe, molestation by a parent and financial problems. Such a profile should be constructed in a way that it is easy to apply and it should be thoroughly tested for substantial predictive value. For example, it could be conceptualized as a risk-flowchart, in which each risk factor adds points and a total score indicates the total estimated risk for mental health problems. Such a risk-flowchart could be applied to identify adolescents at increased risk for mental health problems and serve targeted prevention strategies. Settings that could profit from such a screening instrument include

schools and universities, community health service centers and the general practitioner. Furthermore, complementing the focus on risk factors, clinical practice could also benefit from the identification of protective factors. Factors that seem likely to prevent mental health problems, include good attachment to the parents or significant others, pro-social involvement at home and in school and good cooperation skills.

Implications for clinical practice

The results of this thesis may be helpful for teachers, tutors, school psychologists and -nurses, general practitioners, as well as therapists and health care workers in hospitals and other institutions providing mental health care. The results show that intensity and frequency of cannabis use play an important role: having used cannabis just once does not increase the risk for mental health problems for the majority of people. Only if cannabis use is started before the age of 15 years or the frequency exceeds monthly or even weekly, further assessment of wellbeing is warranted. This assessment should have a specific focus on concomitant other risk factors.

The results in this thesis do not support the notion of monthly cannabis use as a cause of general mental health problems in young adults. Therefore, a reduction in cannabis intake would not lead to a reduction in mental health problems. Rather, cannabis use *possibly*, but not necessarily, reflects an increased mental vulnerability. This vulnerability could be due to a genetic predisposition for mental health problems, a multitude of other risk factors, or both. When an individual uses cannabis, it is important to assess these other risk factors by inquiring after mental health problems of relatives, socio-economic status, traumatic experiences, the reason for using cannabis and so on.

Heavy and early cannabis use, at a frequency of at least weekly and before the age of 15 years, *do* seem to pose an additional risk, especially for psychotic symptoms. If a young adolescent states to have used more than once, or an adult states to have used cannabis more than once before the age of 15 and/or more than weekly at present, specific attention should be paid to psychotic symptoms.

Implications for policy

The main conclusions of this thesis could help promote a more balanced view of the association between cannabis use and mental health problems. Based on its results, prevention strategies aimed at young and heavy users could be of avail in reducing psychotic symptoms. However, the results of this thesis imply that strategies designed to diminish cannabis use in general, disregarding coinciding risk factors, would not lead to improved public mental health. If moderate cannabis use is indeed a mere indicator of risk as opposed to a cause of mental health problems, diminishing it would not lead to a

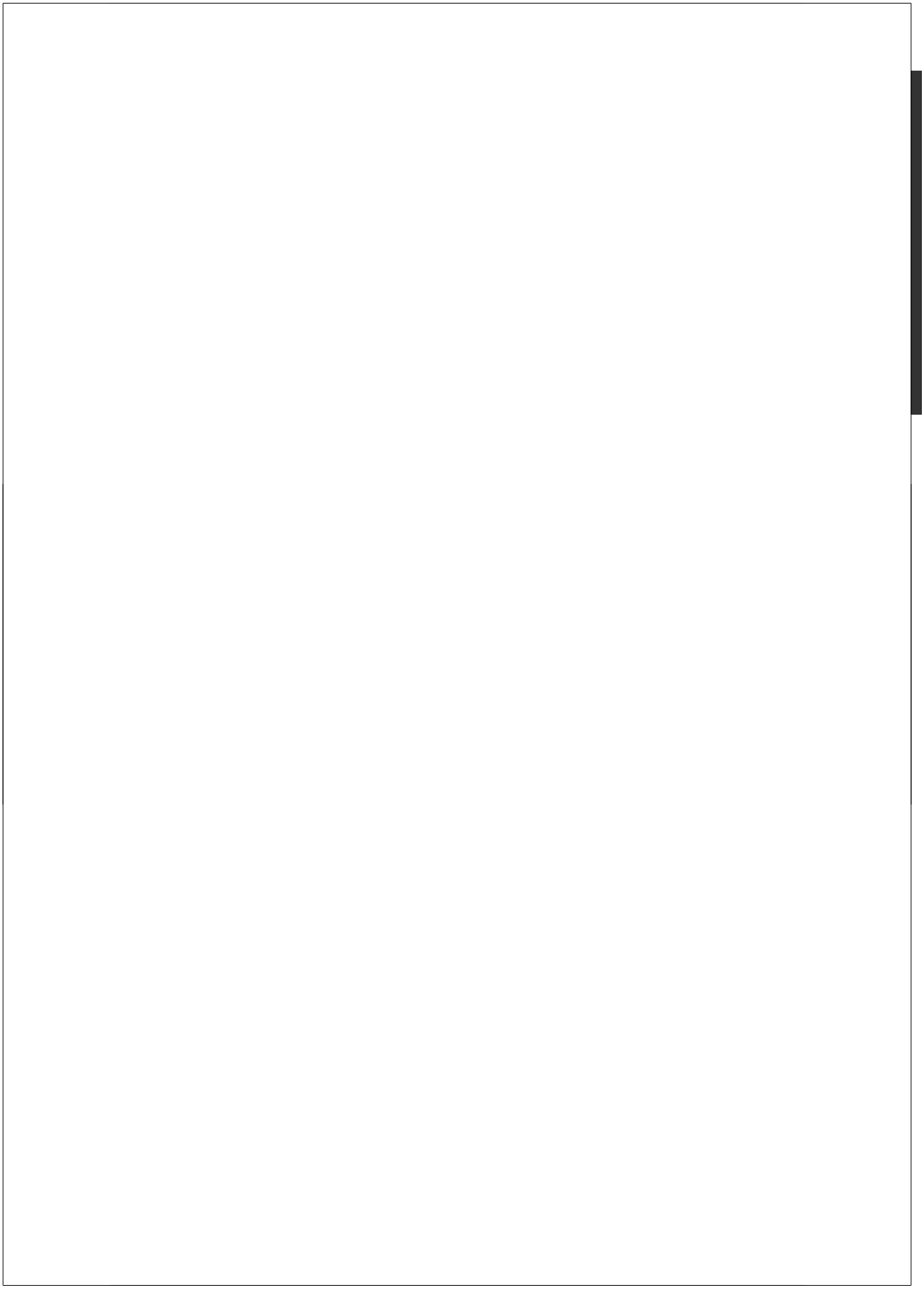
reduction of the risk because the cause(s) remain(s)- be it an innate mental vulnerability or the impact of risk factors (e.g. low socio-economic status, being bullied, foreign ethnicity and traumatic experiences). Instead, moderate cannabis use should be seen as a 'red flag', calling for raised awareness for mental health problems. The results in this thesis suggest that the association between moderate cannabis use and poor general mental health, as opposed to psychotic symptoms, is a-specific. This indicates that use of any substance (including tobacco) should be viewed as an indicator of elevated risk for mental health problems in general.

Regarding the specific case of prevention of psychotic symptoms and schizophrenia, which is often cited as an important aim for policies, targeting cannabis use does not seem to be a cost-effective strategy. In 2009, Hickman and colleagues calculated that more than 5 000 men and almost 10 000 women, respectively, should be kept from cannabis use in order to prevent one case of psychosis (Hickman *et al.* 2009).

Of note in this respect is the lack of evidence that criminalization reduces cannabis use, or that decriminalization increases cannabis use (Reinarman *et al.* 2004; Degenhardt *et al.* 2007; Lloyd, 2008; Greenwald, 2009). Apart from the lack of impact of prohibition on consumption levels, levels of drug law enforcement have been found to correlate with drug-related violence and it has been stated that from a mental health perspective, the harms attributable to cannabis prohibition (i.e. drug-related violence) may well exceed the harms associated with the actual use of cannabis (Werb *et al.* 2010). Mental health policies would benefit most from (research into) strategies implementing regular use of cannabis as a risk indicator for increased vulnerability for mental health problems.

CONCLUSION

Taken together, the results of the studies presented in this thesis suggest that mentally vulnerable individuals are more inclined towards cannabis use. This implicates that cannabis use per se is best viewed as an indicator of risk for mental health; regardless of whether this risk is caused by an innate predisposition towards mental health problems, a reflection of adverse effects of a multitude of risk factors, or both. However, the results also point towards additionally increased psychosis proneness especially when cannabis use is initiated before the age of 15 years or the frequency of use exceeds once per week.



8 Nederlandse Samenvatting

Cannabis (ook wel bekend als Marijuana, Wiet, Bambalabacha, Hasj, Kaya, Dope, Marimba, Pot…) is één van de oudste en meest populaire psycho-actieve middelen in de wereld. De vroegste archeologische vondsten dateren terug tot 10.000 jaar voor Christus en de eerste beschrijving van de psycho-actieve eigenschappen stamt uit 2.700 jaar voor Christus (Childers & Breivogel, 1998). Tegenwoordig is het wereldwijd de meestgebruikte drug (European Monitoring Centre for Drugs and Drug Addiction, 2012). Tot ongeveer 1850 werd cannabis (in de vorm van hennep) in de Westerse wereld vooral gezien als een waardevolle grondstof voor kleding, papier en de zeilen en lijnen van schepen. Vanaf het moment dat de psycho-actieve eigenschappen van de cannabisplant hier bekend werden, heeft het extreme reacties opgeroepen: van gebruikers die de geestverruimende werking prijzen, tot tegenstanders die het middel veroordelen op grond van morele, politieke en sociale argumenten.

Dit proefschrift voorziet het cannabisdebat van wetenschappelijke argumenten, met een speciale focus op de adolescentie en de jonge volwassenheid. In deze Nederlandse samenvatting worden de belangrijkste bevindingen van dit onderzoek beschreven, evenals de praktische implicaties.

CANNABISGEBRUIK EN ALGEMENE PSYCHISCHE PROBLEMEN

De studies in dit proefschrift die zich richten op algemene psychische problemen, maken gebruik van vragenlijsten die ontworpen zijn om het algehele psychische functioneren in kaart te brengen. Voor jonge adolescenten werd daarbij gekeken naar emotionele problemen, hyperactiviteit, antiscociaal gedrag en problemen met leeftijdsgenoten. Voor jongvolwassenen werd gekeken naar klachten op gebied van angst, depressie, somatisatie, dwang en obsessies, interpersoonlijke overgevoeligheid, vijandigheid en achterdocht.

In **Hoofdstuk 2** werd de samenhang tussen cannabisgebruik en psychosociaal functioneren bestudeerd in een grote steekproef van middelbare scholieren in de leeftijd van 11 tot 16 jaar in de regio Utrecht, in samenwerking met GGD regio Utrecht. Cannabisgebruikers bleken een verviervoudigd risico te hebben op psychische problemen. Er was echter geen dosis-respons effect. Bovendien werd dit verhoogde risico *niet* verklaard door cannabisgebruik zelf, maar doordat cannabisgebruik vaak voorkwam in combinatie met andere risicofactoren. Er bleek een grote overlap te zijn tussen de risicofactoren voor psychische gezondheid en die voor cannabisgebruik; regelmatig alcoholgebruik, roken, harddrugs gebruik, regelmatig spijbelen, school niet leuk vinden en regelmatig afwezig zijn door ziekte vergrootten zowel de kans op psychische problemen als die op cannabisgebruik. Deze bevindingen wijzen erop dat de samenhang tussen cannabisgebruik en psychische problemen het beste kan worden verklaard door *confounding*, ofwel door

het feit dat beiden sterk samenhangen met andere factoren en dus indirect verbonden zijn. Een bekend voorbeeld van *confounding* is de samenhang tussen koffiedrinken en longkanker. Koffie is niet de oorzaak van longkanker, maar beiden hangen sterk samen met roken.

Hoofdstuk 4 beschrijft een studie naar de samenhang tussen cannabisgebruik en psychische problemen bij jongvolwassenen (18-30 jaar). Net als in hoofdstuk 2 werd er rekening gehouden met andere risicofactoren voor psychische problemen. Anders dan in die studie, bleef de samenhang tussen cannabisgebruik en psychische problemen in deze studie wel overeind na de correctie voor deze factoren. Dit doet vermoeden dat er een directe relatie tussen deze twee bestaat. De set van risicofactoren waarvoor we konden corrigeren was in deze studie echter veel kleiner, wat *residual confounding* waarschijnlijk maakt. In dat geval wordt de samenhang tussen cannabisgebruik en psychische gezondheid opgeblazen, doordat onbekende factoren ('derde factoren') met beiden samenhangen. Uit deze studie bleek verder een dosis-respons relatie tussen cannabisgebruik en psychische klachten; wekelijkse gebruikers hadden een grotere kans op psychische klachten dan maandelijkse gebruikers. Dit was onafhankelijk van de leeftijd waarop iemand voor het eerst cannabis had gebruikt, en dus niet uitsluitend te wijten aan een blijvend schadelijk effect van vroeggebruik. Verder bleek dat cannabisgebruik bij vrouwen vaker wijst op psychische problemen dan bij mannen.

In beide studies in dit proefschrift naar de samenhang tussen cannabisgebruik en algemene psychische klachten wordt ervoor gepleit cannabis te beschouwen als een risico-indicator van psychische klachten; ongeacht de al dan niet causale aard van de samenhang.

CANNABISGEBRUIK EN PSYCHOTISCHE ERVARINGEN

De studies in dit proefschrift die de samenhang tussen cannabisgebruik en psychotische ervaringen onderzoeken, maken gebruik van de CAPE vragenlijst (*Community Assessment of Psychic Experiences*). Deze vragenlijst is ontworpen om ook milde psychotische klachten in kaart te brengen; vandaar de term 'psychotische *ervaringen*', of *psychotic-like experiences*. Deze term past in het steeds genuanceerdere denken over psychische klachten: in plaats van ziek versus gezond of normaal versus abnormaal, wordt de onderliggende structuur van psychische klachten steeds meer voorgesteld als een continuum, dat in dit geval reikt van de afwezigheid van psychotische symptomen tot een klinische psychose. Psychotische ervaringen liggen ergens op dit continuum; in sommige gevallen zijn zij een voorbode van zwaardere psychotische symptomen, in andere gevallen zijn zij van voorbijgaande aard.

Voorbeelden van psychotische ervaringen zijn: het gevoel hebben dat mensen dingen zeggen met een dubbele betekenis, het idee hebben dat je achtervolgd wordt en geloof in telepathie of het bovennatuurlijke. De vragenlijst meet ervaringen in drie dimensies: positief (ervaringen die 'erbij komen'), negatief (het wegvallen van ervaringen, met name emoties) en depressief.

Hoofdstuk 3 beschrijft een studie onder jonge adolescenten (12-16 jaar) in Nederland, die meededen aan de *Health and Behaviour in School-aged Children* studie van de Wereldgezondheidsorganisatie. Deze studie werd uitgevoerd in samenwerking met de afdeling Sociale Wetenschappen van de Universiteit Utrecht. Deelnemers aan het onderzoek die cannabis gebruikten, gaven vaker aan (milde) positieve psychotische ervaringen te hebben dan deelnemers die dat niet deden. Er was een onafhankelijke dosis-respons relatie: hoe vaker iemand had geblowd, hoe meer positieve psychotische ervaringen hij had. Opvallend was dat jongeren die aangaven meer dan een jaar geleden te hebben gebruikt, maar tegenwoordig niet meer, net zo veel positieve psychotische ervaringen hadden als de jongeren die op dit moment nog zwaar gebruikten (40 keer of vaker in het afgelopen jaar). Deze bevinding is in lijn met de hypothese dat vroeggebruik kan leiden tot een blijvende beschadiging van het zich ontwikkelende brein, die zich uit in een verhoogde kwetsbaarheid voor psychose. Een alternatieve verklaring is dat jongeren die al vroeg in aanraking komen met cannabis ook worden blootgesteld aan een verzameling van andere risicofactoren.

In **hoofdstuk 5** werden twee karakteristieken van cannabisgebruik onderzocht: beginleeftijd (retrospectief) en de intensiteit van gebruik. De laatste werd gemeten aan de hand van het bedrag in euro waarvoor een deelnemer cannabis gebruikte. Omdat de marktwaarde van cannabis in Nederland is gecorreleerd aan het THC gehalte, gaf dit een indicatie van de mate van blootstelling aan THC (Δ-9-tetrahydrocannabinol, het belangrijkste psychoactieve bestanddeel van de cannabisplant). Hoe lager de beginleeftijd, hoe groter de kans op positieve en negatieve psychotische ervaringen. Deelnemers die voor hun twaalfde waren begonnen met blowen hadden een drie maal zo grote kans op positieve psychotische ervaringen ten opzichte van deelnemers die tussen hun vijftiende en hun achttiende waren begonnen. Voor de intensiteit van gebruik werd eenzelfde relatie gevonden: hoe meer iemand gebruikte, hoe groter de kans op psychotische ervaringen in de positieve, negatieve en depressieve dimensie. Deelnemers in de hoogste categorie, gelijk aan meer dan zo'n zeven joints per week, hadden een verdrievoudigde kans op psychotische ervaringen. Voor gebruikers in de op één na hoogste categorie, gelijk aan zo'n drie tot zeven joints per week, was deze kans verdubbeld.

De studie in **hoofdstuk 6** onderzocht of de relatie tussen cannabisgebruik en psychotische ervaringen beïnvloed wordt door het roken van sigaretten. Roken bleek een even sterke relatie te hebben met de frequentie van psychotische ervaringen als maandelijks blowen, en zelfs sterker met de mate waarin iemand aangaf verontrust te raken door die ervaringen. Deze bevinding is belangrijk, omdat de mate waarin iemand verontrust raakt door zijn of haar psychotische ervaringen een van de belangrijkste voorspellers is voor een ongunstig beloop. De resultaten wijzen erop dat de relatie tussen maandelijks blowen en psychotische ervaringen sterk beïnvloed wordt door roken en dat mensen die een aanleg hebben tot psychotische ervaringen eerder geneigd zijn te gaan roken en blowen. Voor wekelijks cannabisgebruik echter, was er een onafhankelijke relatie met psychotische ervaringen. Dit wijst erop dat de frequentie van gebruik een sleutelrol kan spelen in de relatie met psychotische ervaringen; mogelijk treedt een causaal verband pas in werking bij een frequentie van wekelijks of meer.

Samengenomen wijzen de studies naar psychotische ervaringen in dit proefschrift erop dat de samenhang met matig cannabisgebruik het resultaat is van reeds bestaande kwetsbaarheid, in de vorm van een aanleg voor psychotische ervaringen of door een verzameling van andere risicofactoren, die op hun beurt samenhangen met cannabisgebruik. Voor vroeg en zwaar gebruik echter, zijn er overtuigende aanwijzingen dat deze wel degelijk kunnen leiden tot een verhoogd risico op psychotische ervaringen.

PRAKTISCHE IMPLICATIES

De bevindingen in dit proefschrift kunnen gebruikt worden door docenten, mentoren, schoolpsychologen, huisartsen, psychologen, psychiaters, SPV'ers en andere welzijnswerkers. Uit dit onderzoek blijkt dat de intensiteit en frequentie van gebruik een sleutelrol spelen: eenmalig gebruik van cannabis vergroot het risico op psychische problemen voor de meerderheid van de mensen niet. Alleen een aanvang van gebruik voor het 15^{e} jaar of een frequentie hoger dan maandelijks of zelfs wekelijks vraagt om nader onderzoek. Daarbij moet met name aandacht besteed worden aan de aanwezigheid van andere risicofactoren.

De bevindingen in dit proefschrift geven geen steun aan het idee dat maandelijks cannabisgebruik een oorzaak is van psychische problemen. Een vermindering van cannabisgebruik zou dus ook niet leiden tot een vermindering van psychische klachten. Cannabisgebruik wijst *mogelijk,* maar niet *noodzakelijk* op een psychische kwetsbaarheid. Deze kwetsbaarheid kan het gevolg zijn van genetische aanleg, de aanwezigheid van

een verzameling andere risicofactoren, of beiden. Als iemand cannabis gebruikt, is het belangrijk om de andere risicofactoren goed in beeld te krijgen, bijvoorbeeld door te vragen naar de psychische gezondheid van familieleden, sociaal-economische status, traumatische ervaringen en de reden voor het cannabisgebruik.

Zwaar (meer dan wekelijks) en vroeg (voor het 15e jaar) gebruik lijken echter wel degelijk de kans op psychische klachten te vergroten, met name psychotische. Als een jongere onder de 15 aangeeft te hebben geblowd, of een volwassene aangeeft te zijn gestart voor zijn 15e of meer dan wekelijks te gebruiken, moet er extra gelet worden op psychotische ervaringen.

IMPLICATIES VOOR BELEID

De bevindingen in dit proefschriften kunnen bijdragen aan een genuanceerder beeld over de relatie tussen cannabisgebruik en psychische problemen. De uitkomsten laten zien dat preventiestrategieën die zich richten op zwaar en vroeg gebruik kunnen helpen in het verminderen van de prevalentie van psychotische ervaringen. De resultaten impliceren echter ook dat strategieën die ontworpen zijn om cannabisgebruik in zijn algemeenheid te laten afnemen, zonder het in ogenschouw nemen van andere risicofactoren, niet zouden leiden tot een verbetering van de algemene volksgezondheid. Als matig cannabisgebruik inderdaad slechts een risico-indicator is, in plaats van een oorzaak van psychische problemen, zou een afname in gebruik niet leiden tot een afname in klachten. De werkelijke oorzaak van de klachten wordt daarmee immers niet weggenomen: of dat nu een aangeboren kwetsbaarheid is of het gevolg van andere risicofactoren. Cannabisgebruik kan beter beschouwd worden als een rode vlag, die *mogelijk* wijst op een vergrote psychische kwetsbaarheid. De bevindingen in dit proefschrift suggereren dat de relatie tussen cannabis en algemene psychische problemen aspecifiek is. Dat betekent dat het gebruik van welk psycho-actief middel dan ook, inclusief tabak, gezien moet worden als een indicator van verhoogd risico op algemene psychische problemen.

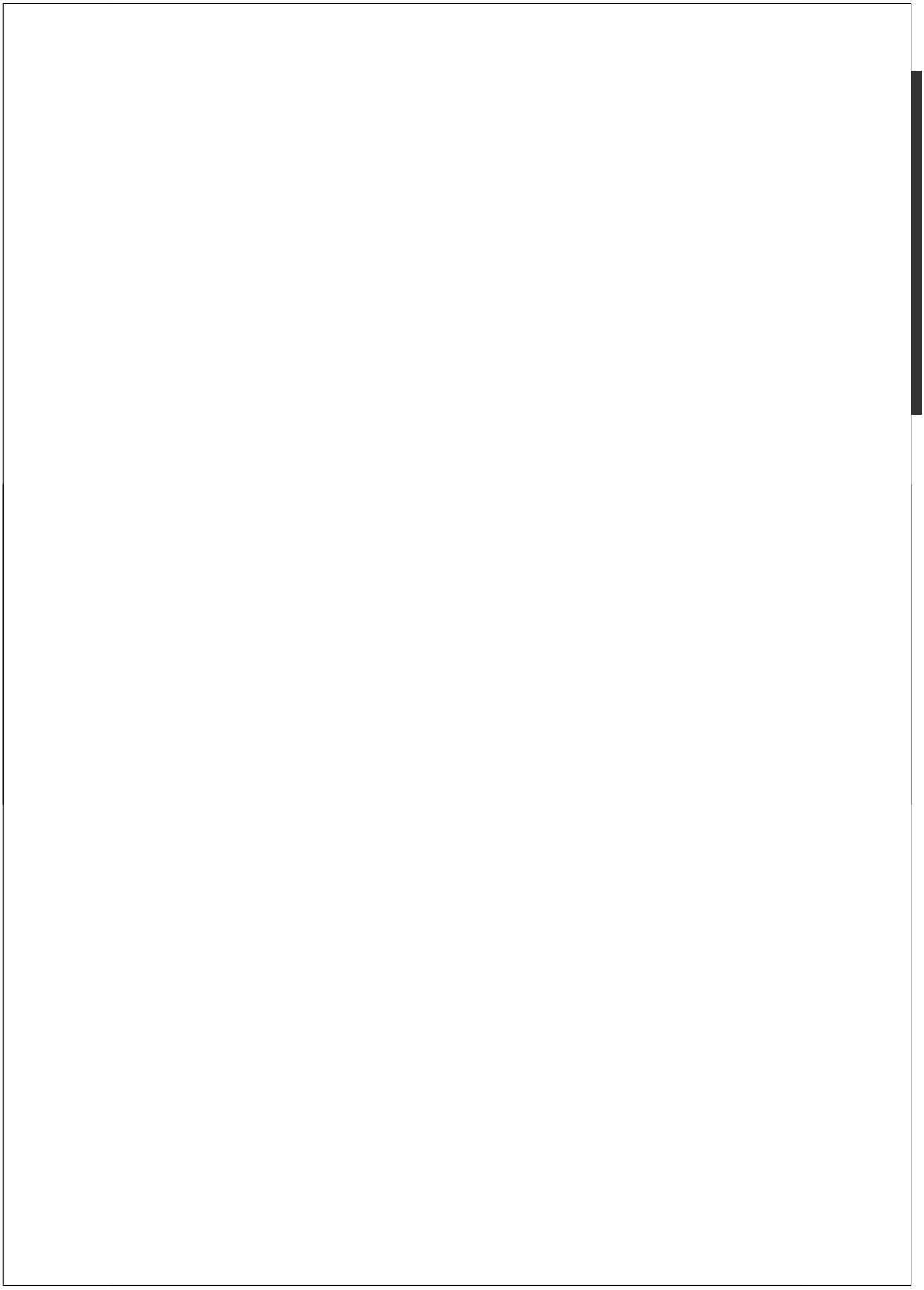
Voor de preventie van psychotische symptomen en schizofrenie, vaak een belangrijk beleidsdoel, lijkt een focus op cannabisgebruik niet kosten-effectief. In 2009 berekenden Hickman en collega's dat er meer dan 5.000 mannen of bijna 10.000 vrouwen van cannabisgebruik zouden moeten worden weerhouden om één persoon voor een psychose te behoeden (Hickman *et al.*, 2009).

Een ander belangrijk punt voor het beleid rondom cannabis is het gebrek aan bewijs dat cannabisgebruik afneemt als het strafbaar wordt gesteld en omgekeerd dat decriminalisatie leidt tot een toename in gebruik (Reinarman *et a*l., 2004; Degenhardt

et al., 2007; Lloyd, 2008; Greenwald, 2009). Naast het uitblijven van een effect op gebruikersaantallen, blijkt een strengere handhaving van een wettelijk verbod ook te leiden tot een toename in drugs-gerelateerd geweld. Er gaan zelfs stemmen op die zeggen dat vanuit een volksgezondheidsperspectief de nadelige effecten van een verbod op cannabisgebruik groter zijn dan de nadelige effecten van het cannabisgebruik zelf (Werb *et al.*, 2010). Beleid gericht op een verbetering van de geestelijke volksgezondheid zou het meest gebaat zijn bij onderzoek naar strategieën die regelmatig cannabisgebruik toepassen als een risico-indicator voor een verhoogde kans op psychische problemen.

CONCLUSIE

Samengenomen wijzen de bevindingen in dit proefschrift erop dat psychisch kwetsbare personen sneller geneigd zijn cannabis te gebruiken. Cannabisgebruik kan zodoende het beste gezien worden als een indicator van een verhoogd risico op psychische problemen; ongeacht of dit risico voortkomt uit genetische aanleg, een verzameling van risicofactoren, of beide. Als er specifiek wordt gekeken naar psychotische symptomen, zijn er echter wel degelijk aanwijzingen dat een aanvang voor het 15^{e} levensjaar of een frequentie van meer dan wekelijks het risico op klachten vergroot.



9 References

Adlaf, E. M., Begin, P. & Sawka, E. (2005). *Canadian Addiction Survey (CAS):A national survey of Canadians' use of alcohol and other drugs: Prevalence of use and related harms: Detailed report*. Canadian Centre on Substance Abuse: Ottawa.

Agrawal, A., Budney, A. J. & Lynskey, M. T. (2012). The co-occurring use and misuse of cannabis and tobacco: a review. *Addiction* **107**, 1221-1233.

Andreasson, S., Allebeck, P., Engstrom, A. & Rydberg, U. (1987a). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* **2**, 1483-1486.

Anslinger, H. J. (1937). *Hearing for the American House of Representatives on the Marijuana Tax Act (April-May 1937)*. In (http://www.druglibrary.org/schaffer/hemp/taxact/anslng1.htm), accessed 19th of November 2012.

Arrindell, W. A. & Ettema, J. H. M. (2005). *Symptom-checklist 90 Handleiding bij een multidimensionale psychopathologie-indicator*. Harcourt Assessment: Amsterdam.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A. & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* **325**, 1212-1213.

Balter, K. A., Balter, O., Fondell, E. & Lagerros, Y. T. (2005). Web-based and mailed questionnaires: a comparison of response rates and compliance. *Epidemiology* **16**, 577-579.

Barr, R. S., Culhane, M. A., Jubelt, L. E., Mufti, R. S., Dyer, M. A., Weiss, A. P., Deckersbach, T., Kelly, J. F., Freudenreich, O., Goff, D. C. & Evins, A. E. (2008). The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology* **33**, 480-490.

Baudelaire, C. (1860). *Les Paradis Artificiels*. Chapter IV - Le Haschisch. In (http://baudelaire.litteratura.com), accessed 19th of November 2012.

Boks, M. P. (2012). Progress in gene environment studies. *Biol. Psychiatry* **72**, 799-800.

Bossong, M. G. & Niesink, R. J. (2010). Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Prog. Neurobiol.* **92**, 370-385.

Bovasso, G. B. (2001). Cannabis abuse as a risk factor for depressive symptoms. *Am. J. Psychiatry* **158**, 2033-2037.

Breivogel, C. S. & Childers, S. R. (1998). The functional neuroanatomy of brain cannabinoid receptors. *Neurobiol. Dis.* **5**, 417-431.

Brody, A. L., Olmstead, R. E., London, E. D., Farahi, J., Meyer, J. H., Grossman, P., Lee, G. S., Huang, J., Hahn, E. L. & Mandelkern, M. A. (2004). Smoking-induced ventral striatum dopamine release. *Am. J. Psychiatry* **161**, 1211-1218.

Brook, J. S., Cohen, P. & Brook, D. W. (1998). Longitudinal study of co-occurring psychiatric disorders and substance use. *J. Am. Acad. Child Adolesc. Psychiatry* **37**, 322-330.

Buchanan, T. & Smith, J. L. (1999). Using the Internet for psychological research: personality testing on the World Wide Web. *Br. J. Psychol.* **90**, 125-144.

Buckner, J. D., Bonn-Miller, M. O., Zvolensky, M. J. & Schmidt, N. B. (2007). Marijuana use motives and social anxiety among marijuana-using young adults. *Addict. Behav.* **32**, 2238-2252.

Buckner, J. D., Ecker, A. H. & Vinci, C. (2012). Cannabis Use Vulnerability Among Socially Anxious Users: Cannabis Craving During a Social Interaction. *Psychol. Addict. Behav. Epub September 24 2012*

Cantor-Graae, E. & Selten, J. P. (2005). Schizophrenia and migration: a meta-analysis and review. *Am. J. Psychiatry* **162**, 12-24.

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R. & Craig, I. W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol. Psychiatry* **57**, 1117-1127.

CBS Statistics Netherlands (2008). Bijna evenveel hoogopgeleide als laagopgeleide Nederlanders. In (www.CBS.nl Webmagazine; art 2436).

CBS Statistics Netherlands (2009). Persbericht: Mediaproducten steeds meer via internet. In (www.CBS.nl Report number PB08-071).

Cha, Y. M., White, A. M., Kuhn, C. M., Wilson, W. A. & Swartzwelder, H. S. (2006). Differential effects of delta9-THC on learning in adolescent and adult rats. *Pharmacol. Biochem. Behav.* **83**, 448-455.

Chapman, L. J., Chapman, J. P., Kwapil, T. R., Eckblad, M. & Zinser, M. C. (1994). Putatively psychosis-prone subjects 10 years later. *J. Abnorm. Psychol.* **103**, 171-183.

Charach, A., Yeung, E., Climans, T. & Lillie, E. (2011). Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. *J. Am. Acad. Child Adolesc. Psychiatry* **50**, 9-21.

Chaves, S. S., Gargiullo, P., Zhang, J. X., Civen, R., Guris, D., Mascola, L. & Seward, J. F. (2007). Loss of Vaccine-Induced Immunity to Varicella over Time. *New England Journal of Medicine* **356**, 1121-1129.

Cheetham, A., Allen, N. B., Whittle, S., Simmons, J. G., Yucel, M. & Lubman, D. I. (2012). Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study. *Biol. Psychiatry* **71**, 684-692.

Chevaleyre, V., Takahashi, K. A. & Castillo, P. E. (2006). Endocannabinoid-mediated synaptic plasticity in the CNS. *Annu. Rev. Neurosci.* **29**, 37-76.

Childers, S. R. & Breivogel, C. S. (1998). Cannabis and endogenous cannabinoid systems. *Drug Alcohol Depend.* **51**, 173-187.

Coles, M. E., Cook, L. M. & Blake, T. R. (2007). Assessing obsessive compulsive symptoms and cognitions on the internet: evidence for the comparability of paper and Internet administration. *Behav. Res. Ther.* **45**, 2232-2240.

Compton, M. T., Kelley, M. E., Ramsay, C. E., Pringle, M., Goulding, S. M., Esterberg, M. L., Stewart, T. & Walker, E. F. (2009). Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. *Am. J. Psychiatry* **166**, 1251-1257.

Costas, J., Sanjuan, J., Ramos-Rios, R., Paz, E., Agra, S., Tolosa, A., Paramo, M., Brenlla, J. & Arrojo, M. (2011). Interaction between COMT haplotypes and cannabis in schizophrenia: a case-only study in two samples from Spain. *Schizophr. Res.* **127**, 22-27.

Cougnard, A., Marcelis, M., Myin-Germeys, I., De Graaf R., Vollebergh, W., Krabbendam, L., Lieb, R., Wittchen, H. U., Henquet, C., Spauwen, J. & van Os, J. (2007). Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychol. Med.* **37**, 513-527.

Cuijpers, P., Boluijt, P. & van Straten, A. (2008). Screening of depression in adolescents through the Internet : sensitivity and specificity of two screening questionnaires. *Eur. Child Adolesc. Psychiatry* **17**, 32-38.

Currie, C., Samdal, O., Boyce, W., Smith, R., Settertobulte, W. & Barnekow Rasmussen, V. (2001). Health Behaviour in school-aged children: a World Health Organization Cross-National Study. Research protocol for the 2001/02 Survey. Edinburgh: University of Edinburgh, Child and Adolescent Health Research Unit.

Currie, C. E., Elton, R. A., Todd, J. & Platt, S. (1997). Indicators of socioeconomic status for adolescents: the WHO Health Behaviour in School-aged Children Survey. *Health Educ. Res.* **12**, 385-397.

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., Braley, G., Gueorguieva, R. & Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* **29**, 1558-1572.

Dalack, G. W., Healy, D. J. & Meador-Woodruff, J. H. (1998). Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. *Am. J. Psychiatry* **155**, 1490-1501.

Dalack, G. W. & Meador-Woodruff, J. H. (1996). Smoking, smoking withdrawal and schizophrenia: case reports and a review of the literature. *Schizophr. Res.* **22**, 133-141.

De Beer, H. & van de Glind, G. (2009). *Richtlijn Multidisciplinaire stoornissen in het gebruik van alcohol*. In (www.cbo.nl/Downloads/206/rl_alcohol_09.pdf) accessed 19th of November 2012. Ladenius Communicatie, CBO/Trimbos Institute: Houten.

Dean, B., Bymaster, F. P. & Scarr, E. (2003). Muscarinic receptors in schizophrenia. *Curr. Mol. Med.* **3**, 419-426.

Decoster, J., van, Os. J., Myin-Germeys, I., De Hert M. & van Winkel, R. (2012). Genetic Variation Underlying Psychosis-inducing Effects of Cannabis: Critical Review and Future Directions. *Curr. Pharm. Des* **18**, 5015-5023.

Degenhardt, L. & Hall, W. (2001). The relationship between tobacco use, substance-use disorders and mental health: results from the National Survey of Mental Health and Well-being. *Nicotine. Tob. Res.* **3**, 225-234.

Degenhardt, L., Hall, W. & Lynskey, M. (2001). Alcohol, cannabis and tobacco use among Australians: a comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis. *Addiction* **96**, 1603-1614.

Degenhardt, L., Hall, W. & Lynskey, M. (2003). Exploring the association between cannabis use and depression. *Addiction* **98**, 1493-1504.

Degenhardt, L., Hall, W. D., Roxburgh, A. & Mattick, R. P. (2007). UK classification of cannabis: is a change needed and why? *Lancet* **370**, 1541.

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E. H. & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav. Sci.* **19**, 1-15.

Dhossche, D., Ferdinand, R., van der, E. J., Hofstra, M. B. & Verhulst, F. (2002). Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. *Psychol. Med.* **32**, 619-627.

Di Forti, M., Iyegbe, C., Sallis, H., Kolliakou, A., Falcone, M. A., Paparelli, A., Sirianni, M., La Cascia, C., Stilo, S. A., Marques, T. R., Handley, R., Mondelli, V., Dazzan, P., Pariante, C., David, A. S., Morgan, C., Powell, J. & Murray, R. M. (2012). Confirmation that the AKT1 (rs2494732) Genotype Influences the Risk of Psychosis in Cannabis Users. *Biol. Psychiatry* **72**, 811-816.

Dominguez, M. D., Wichers, M., Lieb, R., Wittchen, H. U. & van Os, J. (2011). Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophr. Bull.* **37**, 84-93.

Donker, T., van, S. A., Marks, I. & Cuijpers, P. (2009). Brief self-rated screening for depression on the Internet. *J. Affect. Disord.* **122**, 253-259.

Ehrenreich, H., Rinn, T., Kunert, H. J., Moeller, M. R., Poser, W., Schilling, L., Gigerenzer, G. & Hoehe, M. R. (1999). Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology (Berl)* **142**, 295-301.

Ekman, A., Dickman, P. W., Klint, A., Weiderpass, E. & Litton, J. E. (2006). Feasibility of using web-based questionnaires in large population-based epidemiological studies. *Eur. J. Epidemiol.* **21**, 103-111.

Emerson, E., McCulloch, A., Graham, H., Blacher, J., Llwellyn, G. M. & Hatton, C. (2010). Socioeconomic circumstances and risk of psychiatric disorders among parents of children with early cognitive delay. *Am. J. Intellect. Dev. Disabil.* **115**, 30-42.

European Monitoring Centre for Drugs and Drug Addiction (2012). *Data: Statistical Bulletin 2012*. In (http://www.emcdda.europa.eu/stats12), accessed 19th of November 2012.

European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA) (2008). *2008 Annual report: the state of the drugs problem in Europe*. In (http://www.emcdda.europa.eu/publications/annual-report/2008), accessed 19th of November 2012.

European School Survey Project on Alcohol and Other Drugs (2012). *Summary 2011 ESPAD Report*. European Monitoring Centre for Drugs and Drug Addiction, Publications Office European Union: Lisbon/Luxembourg.

Fattore, L. & Fratta, W. (2010). How important are sex differences in cannabinoid action? *Br. J. Pharmacol.* **160**, 544-548.

Ferdinand, R. F. & Verhulst, F. C. (1994). The prediction of poor outcome in young adults: comparison of the Young Adult Self-Report, the General Health Questionnaire and the Symptom Checklist. *Acta Psychiatr. Scand.* **89**, 405-410.

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

Fergusson, D. M., Horwood, L. J. & Swain-Campbell, N. R. (2003). Cannabis dependence and psychotic symptoms in young people. *Psychol. Med.* **33**, 15-21.

Fergusson, D. M., Lynskey, M. T. & Horwood, L. J. (1993). Conduct problems and attention deficit behaviour in middle childhood and cannabis use by age 15. *Aust. N. Z. J. Psychiatry* **27**, 673-682.

Fernandez-Ruiz, J., Berrendero, F., Hernandez, M. L. & Ramos, J. A. (2000). The endogenous cannabinoid system and brain development. *Trends Neurosci.* **23**, 14-20.

Fischer, B., Rehm, J. & Hall, W. (2009). Cannabis use in Canada: the need for a 'public health' approach. *Can. J. Public Health* **100**, 101-103.

Fontes, M. A., Bolla, K. I., Cunha, P. J., Almeida, P. P., Jungerman, F., Laranjeira, R. R., Bressan, R. A. & Lacerda, A. L. (2011). Cannabis use before age 15 and subsequent executive functioning. *Br. J. Psychiatry* **198**, 442-447.

Fox, C. L., Towe, S. L., Stephens, R. S., Walker, D. D. & Roffman, R. A. (2011). Motives for cannabis use in high-risk adolescent users. *Psychol. Addict. Behav.* **25**, 492-500.

Galera, C., Bouvard, M. P., Melchior, M., Chastang, J. F., Lagarde, E., Michel, G., Encrenaz, G., Messiah, A. & Fombonne, E. (2010). Disruptive symptoms in childhood and adolescence and early initiation of tobacco and cannabis use: the Gazel Youth study. *Eur. Psychiatry* **25**, 402-408.

Garcia-Gil, L., de, M. R., Munoz, R. M., Cebeira, M., Villanua, M. A., Ramos, J. A. & Fernandez-Ruiz, J. J. (1997). Perinatal delta(9)-tetrahydrocannabinol exposure alters the responsiveness of hypothalamic dopaminergic neurons to dopamine-acting drugs in adult rats. *Neurotoxicol. Teratol.* **19**, 477-487.

Garcia-Gil, L., de, M. R., Romero, J., Perez, A., Ramos, J. A. & Fernandez-Ruiz, J. J. (1999). Perinatal delta9-tetrahydrocannabinol exposure augmented the magnitude of motor inhibition caused by GABA(B), but not GABA(A), receptor agonists in adult rats. *Neurotoxicol. Teratol.* **21**, 277-283.

Glass, M., Dragunow, M. & Faull, R. L. (1997). Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* **77**, 299-318.

Goodman, A. (2010). Substance use and common child mental health problems: examining longitudinal associations in a British sample. *Addiction* **105**, 1484-1496.

Goodman, R., Meltzer, H. & Bailey, V. (1998). The Strengths and Difficulties Questionnaire: a pilot study on the validity of the self-report version. *Eur. Child Adolesc. Psychiatry* **7**, 125-130.

Goodman, R., Renfrew, D. & Mullick, M. (2000). Predicting type of psychiatric disorder from Strengths and Difficulties Questionnaire (SDQ) scores in child mental health clinics in London and Dhaka. *Eur. Child Adolesc. Psychiatry* **9**, 129-134.

Gosling, S. D., Vazire, S., Srivastava, S. & John, O. P. (2004). Should we trust web-based studies? A comparative analysis of six preconceptions about internet questionnaires. *Am. Psychol.* **59**, 93-104.

Graham, A. L. & Papandonatos, G. D. (2008). Reliability of internet- versus telephone-administered questionnaires in a diverse sample of smokers. *J. Med. Internet. Res.* **10**, e8.

Graham, A. L., Papandonatos, G. D., Bock, B. C., Cobb, N. K., Baskin-Sommers, A., Niaura, R. & Abrams, D. B. (2006). Internet- vs. telephone-administered questionnaires in a randomized trial of smoking cessation. *Nicotine. Tob. Res.* **8 Suppl 1**, S49-S57.

Greenland, S. (1989). Modeling and variable selection in epidemiologic analysis. *Am. J. Public Health* **79**, 340-349.

Greenwald, G. (2009). *Drug Decriminalization in Portugal: Lessons for Creating Fair and Successful Drug Policies*. In (www.cato.org/pubs/wtpapers/greenwald_whitepaper.pdf) accessed 19th of November 2012. CATO Institute: Washington.

Gregg, L., Barrowclough, C. & Haddock, G. (2007). Reasons for increased substance use in psychosis. *Clin. Psychol. Rev.* **27**, 494-510.

GROUP researchers (2011). Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. *Arch. Gen. Psychiatry* **68**, 138-147.

Hanssen, M., Bak, M., Bijl, R., Vollebergh, W. & van Os, J. (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *Br. J. Clin. Psychol.* **44**, 181-191.

Hanssen, M., Peeters, F., Krabbendam, L., Radstake, S., Verdoux, H. & van Os, J. (2003). How psychotic are individuals with non-psychotic disorders? *Soc. Psychiatry Psychiatr. Epidemiol.* **38**, 149-154.

Hayatbakhsh, M. R., McGee, T. R., Bor, W., Najman, J. M., Jamrozik, K. & Mamun, A. A. (2008). Child and adolescent externalizing behavior and cannabis use disorders in early adulthood: an Australian prospective birth cohort study. *Addict. Behav.* **33**, 422-438.

Hayatbakhsh, M. R., Najman, J. M., Jamrozik, K., Mamun, A. A., Alati, R. & Bor, W. (2007). Cannabis and anxiety and depression in young adults: a large prospective study. *J. Am. Acad. Child Adolesc. Psychiatry* **46**, 408-417.

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H. U. & van Os. J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* **330**, 11.

Henquet, C., Murray, R., Linszen, D. & van Os, J. (2005b). The environment and schizophrenia: the role of cannabis use. *Schizophr. Bull.* **31**, 608-612.

Henquet, C., Rosa, A., Krabbendam, L., Papiol, S., Fananas, L., Drukker, M., Ramaekers, J. G. & van Os, J. (2006). An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology* **31**, 2748-2757.

Hernandez, M., Berrendero, F., Suarez, I., Garcia-Gil, L., Cebeira, M., Mackie, K., Ramos, J. A. & Fernandez-Ruiz, J. (2000). Cannabinoid CB(1) receptors colocalize with tyrosine hydroxylase in cultured fetal mesencephalic neurons and their activation increases the levels of this enzyme. *Brain Res.* **857**, 56-65.

Hickman, M., Vickerman, P., Macleod, J., Lewis, G., Zammit, S., Kirkbride, J. & Jones, P. (2009). If cannabis caused schizophrenia--how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. *Addiction* **104**, 1856-1861.

Hides, L., Lubman, D. I., Buckby, J., Yuen, H. P., Cosgrave, E., Baker, K. & Yung, A. R. (2009). The association between early cannabis use and psychotic-like experiences in a community adolescent sample. *Schizophr. Res.* **112**, 130-135.

Hollis, C., Groom, M. J., Das, D., Calton, T., Bates, A. T., Andrews, H. K., Jackson, G. M. & Liddle, P. F. (2008). Different psychological effects of cannabis use in adolescents at genetic high risk for schizophrenia and with attention deficit/hyperactivity disorder (ADHD). *Schizophr. Res.* **105**, 216-223.

Holstein, B. E., Currie, C., Boyce, W., Damsgaard, M. T., Gobina, I., Kokonyei, G., Hetland, J., de Looze, M., Richter, M. & Due, P. (2009). Socio-economic inequality in multiple health complaints among adolescents: international comparative study in 37 countries. *Int. J. Public Health* **54 Suppl 2**, 260-270.

Horwood, L. J., Fergusson, D. M., Hayatbakhsh, M. R., Najman, J. M., Coffey, C., Patton, G. C., Silins, E. & Hutchinson, D. M. (2010). Cannabis use and educational achievement: findings from three Australasian cohort studies. *Drug Alcohol Depend.* **110**, 247-253.

Houston, T. K., Cooper, L. A., Vu, H. T., Kahn, J., Toser, J. & Ford, D. E. (2001). Screening the public for depression through the Internet. *Psychiatr. Serv.* **52**, 362-367.

Husler, G., Plancherel, B. & Werlen, E. (2005). Psychosocial predictors of cannabis use in adolescents at risk. *Prev. Sci.* **6**, 237-244.

Isbell, H., Gorodetzsky, C. W., Jasinski, D., Claussen, U., von Spulak, F. & Korte, F. (1967). Effects of delta-9-trans-tetrahydrocannabinol in man. *Psychopharmacologia.* **11**, 184-188.

Johns, L. C. & van Os, J. (2001). The continuity of psychotic experiences in the general population. *Clin. Psychol. Rev.* **21**, 1125-1141.

Johnston, L. D., O'Malley, P. M., Bachman, J. G. & Schulenberg, J. E. (2009). Monitoring the Future national results on adolescent drug use: Overview of key findings, 2008. In *National Results on Adolescent Drug Use*, pp. 73.

Joinson, A. (1999). Social desirability, anonymity, and Internet-based questionnaires. *Behav. Res. Methods Instrum. Comput.* **31**, 433-438.

Jubelt, L. E., Barr, R. S., Goff, D. C., Logvinenko, T., Weiss, A. P. & Evins, A. E. (2008). Effects of transdermal nicotine on episodic memory in non-smokers with and without schizophrenia. *Psychopharmacology (Berl)* **199**, 89-98.

Karatekin, C., White, T. & Bingham, C. (2010). Shared and nonshared symptoms in youth-onset psychosis and ADHD. *J. Atten. Disord.* **14**, 121-131.

Kelleher, I. & Cannon, M. (2011). Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. *Psychol. Med.* **41**, 1-6.

Kelly, C. & McCreadie, R. G. (1999). Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. *Am. J. Psychiatry* **156**, 1751-1757.

Kendler, K. S., Neale, M. C., MacLean, C. J., Heath, A. C., Eaves, L. J. & Kessler, R. C. (1993). Smoking and major depression. A causal analysis. *Arch. Gen. Psychiatry* **50**, 36-43.

Khazaal, Y., Chatton, A., Cochand, S. & Zullino, D. (2008). Quality of web-based information on cannabis addiction. *J. Drug Educ.* **38**, 97-107.

Koeter, M. W. (1992). Validity of the GHQ and SCL anxiety and depression scales: a comparative study. *J. Affect. Disord.* **24**, 271-279.

Konings, M., Bak, M., Hanssen, M., van Os, J. & Krabbendam, L. (2006). Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. *Acta Psychiatr. Scand.* **114**, 55-61.

Konings, M., Henquet, C., Maharajh, H. D., Hutchinson, G. & van Os, J. (2008). Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad. *Acta Psychiatr. Scand.* **118**, 209-213.

Konings, M., Stefanis, N., Kuepper, R., De Graaf, R., ten, H. M., van Os, J., Bakoula, C. & Henquet, C. (2012). Replication in two independent population-based samples that childhood maltreatment and cannabis use synergistically impact on psychosis risk. *Psychol. Med.* **42**, 149-159.

Korhonen, T., Levalahti, E., Dick, D. M., Pulkkinen, L., Rose, R. J., Kaprio, J. & Huizink, A. C. (2010). Externalizing behaviors and cigarette smoking as predictors for use of illicit drugs: a longitudinal study among Finnish adolescent twins. *Twin. Res. Hum. Genet.* **13**, 550-558.

Krabbendam, L. & van Os, J. (2005). Schizophrenia and urbanicity: a major environmental influence--conditional on genetic risk. *Schizophr. Bull.* **31**, 795-799.

Krishnadas, R., Jauhar, S., Telfer, S., Shivashankar, S. & McCreadie, R. G. (2012). Nicotine dependence and illness severity in schizophrenia. *Br. J. Psychiatry* .

Kuepper, R., van Os, J., Lieb, R., Wittchen, H. U., Hofler, M. & Henquet, C. (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ* **342**, d738.

Landelijk Alcohol en Drugs Informatiesysteem (2011). *LADIS SPECS 2011*. IN (http://www.sivz.nl/ivz-verslavingszorg/ladis/nieuws-en-publicaties/ladis-specs), accessed 19th of November 2012. Stichting Informatievoorziening Zorg: Houten.

Large, M., Sharma, S., Compton, M. T., Slade, T. & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch. Gen. Psychiatry* **68**, 555-561.

Larsson, S., Andreassen, O. A., Aas, M., Rossberg, J. I., Mork, E., Steen, N. E., Barrett, E. A., Lagerberg, T. V., Peleikis, D., Agartz, I., Melle, I. & Lorentzen, S. (2012). High prevalence of childhood trauma in patients with schizophrenia spectrum and affective disorder. *Compr. Psychiatry Epub August 15 2012*.

Lasser, K., Boyd, J. W., Woolhandler, S., Himmelstein, D. U., McCormick, D. & Bor, D. H. (2000). Smoking and mental illness: A population-based prevalence study. *JAMA* **284**, 2606-2610.

Ledgerwood, D. M., Goldberger, B. A., Risk, N. K., Lewis, C. E. & Price, R. K. (2008). Comparison between self-report and hair analysis of illicit drug use in a community sample of middle-aged men. *Addict. Behav.* **33**, 1131-1139.

Lee, S. S., Humphreys, K. L., Flory, K., Liu, R. & Glass, K. (2011). Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin. Psychol. Rev.* **31**, 328-341.

Lev-Ran, S., Imtiaz, S., Taylor, B. J., Shield, K. D., Rehm, J. & le Foll, B. (2012). Gender differences in health-related quality of life among cannabis users: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend.* **123**, 190-200.

Lewis, D. A. (1997). Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology* **16**, 385-398.

Lin, C. C., Bai, Y. M., Liu, C. Y., Hsiao, M. C., Chen, J. Y., Tsai, S. J., Ouyang, W. C., Wu, C. H. & Li, Y. C. (2007). Web-based tools can be used reliably to detect patients with major depressive disorder and subsyndromal depressive symptoms. *BMC. Psychiatry* **7**, 12.

Lloyd, C. (2008). UK cannabis classification: a flawed debate. *Lancet* **371**, 300-301.

Lynskey, M. T., Fergusson, D. M. & Horwood, L. J. (1998). The origins of the correlations between tobacco, alcohol, and cannabis use during adolescence. *J. Child Psychol. Psychiatry* **39**, 995-1005.

Lyon, E. R. (1999). A review of the effects of nicotine on schizophrenia and antipsychotic medications. *Psychiatr. Serv.* **50**, 1346-1350.

Macleod, J., Davey, S. G., Heslop, P., Metcalfe, C., Carroll, D. & Hart, C. (2002). Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. *BMJ* **324**, 1247-1251.

Macleod, J., Davey, S. G., Hickman, M. & Egger, M. (2007). Cannabis and psychosis. *Lancet* **370**, 1539-1540.

Macleod, J. & Hickman, M. (2006). Commentary: understanding pathways to cannabis use and from use to harm. *Int. J. Epidemiol.* **35**, 680-682.

Macleod, J., Oakes, R., Copello, A., Crome, I., Egger, M., Hickman, M., Oppenkowski, T., Stokes-Lampard, H. & Davey, S. G. (2004). Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. *Lancet* **363**, 1579-1588.

Malcolm, C. P., Picchioni, M. M., DiForti, M., Sugranyes, G., Cooke, E., Joseph, C., McQueen, G., Paparelli, A., Stilo, S., O'Connor, J., Morgan, C., Murray, R. M. & Hodgins, S. (2011). Pre-morbid Conduct Disorder symptoms are associated with cannabis use among individuals with a first episode of psychosis. *Schizophr. Res.* **126**, 81-86.

Mattejat, F. & Remschmidt, H. (2008). The children of mentally ill parents. *Dtsch. Arztebl. Int.* **105**, 413-418.

McGee, R., Williams, S., Poulton, R. & Moffitt, T. (2000). A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction* **95**, 491-503.

McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C. & Chant, D. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC. Med.* **2**, 13.

McGrath, J., Welham, J., Scott, J., Varghese, D., Degenhardt, L., Hayatbakhsh, M. R., Alati, R., Williams, G. M., Bor, W. & Najman, J. M. (2010). Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. *Arch. Gen. Psychiatry* **67**, 440-447.

McLaughlin, K. A., Breslau, J., Green, J. G., Lakoma, M. D., Sampson, N. A., Zaslavsky, A. M. & Kessler, R. C. (2011). Childhood socio-economic status and the onset, persistence, and severity of DSM-IV mental disorders in a US national sample. *Soc. Sci. Med.* **73**, 1088-1096.

Mechoulam, R. & Gaoni, Y. (1965). A Total Synthesis of DL-DELTA-1-Tetrahydrocannabinol, the Active Constituent of Hashish. *J. Am. Chem. Soc.* **87**, 3273-3275.

Meyerson, P. & Tryon, W. W. (2003). Validating internet research: a test of the psychometric equivalence of internet and in-person samples. *Behav. Res. Methods Instrum. Comput.* **35**, 614-620.

Miettunen, J., Tormanen, S., Murray, G. K., Jones, P. B., Maki, P., Ebeling, H., Moilanen, I., Taanila, A., Heinimaa, M., Joukamaa, M. & Veijola, J. (2008). Association of cannabis use with prodromal symptoms of psychosis in adolescence. *Br. J. Psychiatry* **192**, 470-471.

Mobascher, A. & Winterer, G. (2008). [Mechanisms of nicotine dependence]. *Pneumologie* **62**, 553-561.

Molina-Holgado, F., Alvarez, F. J., Gonzalez, I., Antonio, M. T. & Leret, M. L. (1997). Maternal exposure to delta 9-tetrahydrocannabinol (delta 9-THC) alters indolamine levels and turnover in adult male and female rat brain regions. *Brain Res. Bull.* **43**, 173-178.

Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M. & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **370**, 319-328.

Morgan, C. D., Wiederman, M. W. & Magnus, R. D. (1998). Discriminant validity of the SCL-90 dimensions of anxiety and depression. *Assessment.* **5**, 197-201.

Morgan, C. J. & Curran, H. V. (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br. J. Psychiatry* **192**, 306-307.

Mortensen, P. B., Pedersen, C. B., Westergaard, T., Wohlfahrt, J., Ewald, H., Mors, O., Andersen, P. K. & Melbye, M. (1999). Effects of family history and place and season of birth on the risk of schizophrenia. *N. Engl. J. Med.* **340**, 603-608.

Mullin, K., Gupta, P., Compton, M. T., Nielssen, O., Harris, A. & Large, M. (2012). Does giving up substance use work for patients with psychosis? A systematic meta-analysis. *Aust. N. Z. J. Psychiatry* **46**, 826-839.

Munro, S., Thomas, K. L. & Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **365**, 61-65.

Muris, P., Meesters, C. & van den Berg, F. (2003). The Strengths and Difficulties Questionnaire (SDQ)--further evidence for its reliability and validity in a community sample of Dutch children and adolescents. *Eur. Child Adolesc. Psychiatry* **12**, 1-8.

Murray, R. M., Morrison, P. D., Henquet, C. & Di Forti, M. (2007). Cannabis, the mind and society: the hash realities. *Nat. Rev. Neurosci.* **8**, 885-895.

Niesink, R., Rigter, S., Hoek, J. & den Boer, N. (2009). *THC-concentraties in wiet, nederwiet en hasj in Nederlands coffeeshops (2008-2009)*. In (http://www.trimbos.nl/webwinkel/productoverzicht-webwinkel/alcohol-en-drugs/af/af0894-thc-concentraties-2008-2009), accessed 21st of November 2012. Trimbos Institute: Utrecht, The Netherlands.

Niesink, R. & van Laar, M. (2012). *THC, CBD en gezondheidseffecten van wiet en hasj*. In (http://www.trimbos.nl/webwinkel/productoverzicht-webwinkel/alcohol-en-drugs/af/~/media/files/gratis%20downloads/af1128%20thc%20cbd%20en%20gezondheidseffecten%20van%20wiet%20en%20hasj.ashx), accessed 19th of November 2012. Trimbos Institute: Utrecht.

O'Hare, T., Shen, C. & Sherrer, M. (2013). Differences in trauma and posttraumatic stress symptoms in clients with schizophrenia spectrum and major mood disorders. *Psychiatry Res.* **205**, 85-95.

O'Shea, M., Singh, M. E., McGregor, I. S. & Mallet, P. E. (2004). Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. *J. Psychopharmacol.* **18**, 502-508.

Obermeier, M., Mayr, A., Schennach-Wolff, R., Seemuller, F., Moller, H. J. & Riedel, M. (2010). Should the PANSS be rescaled? *Schizophr. Bull.* **36**, 455-460.

Patton, G. C., Coffey, C., Carlin, J. B., Degenhardt, L., Lynskey, M. & Hall, W. (2002). Cannabis use and mental health in young people: cohort study. *BMJ* **325**, 1195-1198.

Pedersen, W., Mastekaasa, A. & Wichstrom, L. (2001). Conduct problems and early cannabis initiation: a longitudinal study of gender differences. *Addiction* **96**, 415-431.

Perala, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., Kieseppa, T., Harkanen, T., Koskinen, S. & Lonnqvist, J. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch. Gen. Psychiatry* **64**, 19-28.

Peters, E. R., Joseph, S. A. & Garety, P. A. (1999). Measurement of delusional ideation in the normal population: introducing the PDI (Peters et al. Delusions Inventory). *Schizophr. Bull.* **25**, 553-576.

Poulton, R., Caspi, A., Moffitt, T. E., Cannon, M., Murray, R. & Harrington, H. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch. Gen. Psychiatry* **57**, 1053-1058.

Punnoose, S. & Belgamwar, M. R. (2006). Nicotine for schizophrenia. *Cochrane. Database. Syst. Rev.* CD004838.

Quinn, H. R., Matsumoto, I., Callaghan, P. D., Long, L. E., Arnold, J. C., Gunasekaran, N., Thompson, M. R., Dawson, B., Mallet, P. E., Kashem, M. A., Matsuda-Matsumoto, H., Iwazaki, T. & McGregor, I. S. (2008). Adolescent rats find repeated Delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology* **33**, 1113-1126.

Read, J., van Os., J., Morrison, A. P. & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatr. Scand.* **112**, 330-350.

Reinarman, C., Cohen, P. D. & Kaal, H. L. (2004). The limited relevance of drug policy: cannabis in Amsterdam and in San Francisco. *Am. J. Public Health* **94**, 836-842.

Rey, J. M., Sawyer, M. G., Raphael, B., Patton, G. C. & Lynskey, M. (2002). Mental health of teenagers who use cannabis. Results of an Australian survey. *Br. J. Psychiatry* **180**, 216-221.

Ripoll, N., Bronnec, M. & Bourin, M. (2004). Nicotinic receptors and schizophrenia. *Curr. Med. Res. Opin.* **20**, 1057-1074.

Rossler, W., Hengartner, M. P., Angst, J. & Ajdacic-Gross, V. (2012). Linking substance use with symptoms of subclinical psychosis in a community cohort over 30 years. *Addiction* **107**, 1174-1184.

Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys.* John Wiley & Sons.

Rubino, T., Zamberletti, E. & Parolaro, D. (2012). Adolescent exposure to cannabis as a risk factor for psychiatric disorders. *J. Psychopharmacol.* **26**, 177-188.

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K., Heinimaa, M., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Juckel, G., Heinz, A., Morrison, A., Lewis, S., von Reventlow, H. G. & Klosterkotter, J. (2010). Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Arch. Gen. Psychiatry* **67**, 241-251.

Saha, S., Scott, J. G., Varghese, D., Degenhardt, L., Slade, T. & McGrath, J. J. (2011). The association between delusional-like experiences, and tobacco, alcohol or cannabis use: a nationwide population-based survey. *BMC. Psychiatry* **11**, 202.

Substance Abuse and Mental Health Services Administration (AHMSA) (2007). Results from the 2007 National survey on drug use and health. In (http://store.samhsa.gov/product/Results-from-the-2007-National-Survey-on-Drug-Use-and-Health-NSDUH-National-Findings/SMA08-4343), accessed 21st of November 2012. Rockville, MD: Department of Health and Human Services.

Schneider, M. & Koch, M. (2003). Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology* **28**, 1760-1769.

Schubart, C. D., Boks, M. P., Breetvelt, E. J., van Gastel, W. A., Groenwold, R. H., Ophoff, R. A., Sommer, I. E. & Kahn, R. S. (2011). Association between cannabis and psychiatric hospitalization. *Acta Psychiatr. Scand.* **123**, 368-375.

Schubart C. D., van Gastel W. A., Breetvelt E. J., Beetz S. L., Ophoff R. A., Sommer I. E., Kahn R. S., Boks, M. P. (2010). Cannabis use at a young age is associated with psychotic experiences. *Psychological Medicine* **7,** 1-10.

Selten, J. P., Laan, W., Kupka, R., Smeets, H. M. & van Os. J. (2012). Risk of psychiatric treatment for mood disorders and psychotic disorders among migrants and Dutch nationals in Utrecht, The Netherlands. *Soc. Psychiatry Psychiatr. Epidemiol.* **47**, 271-278.

Skinner, C. J., Holt, D. & Smith, T. M. F. (1989). *Analysis of Complex Surveys.* Wiley: Chichester.

Smit, F., De Zwart, W. M., Spruit, I., Monshouwer, K. & Ameijden, E. (2002). Monitoring substance use in adolescents: school or household survey? *Drugs: Education Prevention and Policy* **9**, 267-274.

Smith, G. D., Phillips, A. N. & Neaton, J. D. (1992). Smoking as "independent" risk factor for suicide: illustration of an artifact from observational epidemiology? *Lancet* **340**, 709-712.

Sorensen, H. J., Mortensen, E. L., Reinisch, J. M. & Mednick, S. A. (2011). A prospective study of smoking in young women and risk of later psychiatric hospitalization. *Nord. J. Psychiatry* **65**, 3-8.

Spek, V., Nyklicek, I., Cuijpers, P. & Pop, V. (2008). Internet administration of the Edinburgh Depression Scale. *J. Affect. Disord.* **106**, 301-305.

Stefanis, N. C., Delespaul, P., Henquet, C., Bakoula, C., Stefanis, C. N. & van Os, J. (2004). Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction* **99**, 1333-1341.

Stefanis, N. C., Hanssen, M., Smirnis, N. K., Avramopoulos, D. A., Evdokimidis, I. K., Stefanis, C. N., Verdoux, H. & van Os. J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychol. Med.* **32**, 347-358.

Steinberg, L. (1999). *Adolescence.* McGraw-Hill Companies: New York.

Stevens, J. P. (2002). *Applied multivariate statistics for the social sciences.* Lawrence Erlbaum Associates: Mahwah, New Jersey; London.

Suarez, I., Bodega, G., Fernandez-Ruiz, J., Ramos, J. A., Rubio, M. & Fernandez, B. (2004). Down-regulation of the AMPA glutamate receptor subunits GluR1 and GluR2/3 in the rat cerebellum following pre- and perinatal delta9-tetrahydrocannabinol exposure. *Cerebellum.* **3**, 66-74.

Swendsen, J., Ben-Zeev, D. & Granholm, E. (2011). Real-time electronic ambulatory monitoring of substance use and symptom expression in schizophrenia. *Am. J. Psychiatry* **168**, 202-209.

Tart, C. T. (1970). Marijuana intoxication common experiences. *Nature* **226**, 701-704.

Termorshuizen, F., Wierdsma, A. I., Visser, E., Drukker, M., Sytema, S., Laan, W., Smeets, H. M. & Selten, J. P. (2012). Psychosis and suicide risk by ethnic origin and history of migration in the Netherlands. *Schizophr. Res.* **138**, 268-273.

Thomas, H. (1996). A community survey of adverse effects of cannabis use. *Drug Alcohol Depend.* **42**, 201-207.

Trezza, V., Cuomo, V. & Vanderschuren, L. J. (2008). Cannabis and the developing brain: insights from behavior. *Eur. J. Pharmacol.* **585**, 441-452.

Trimbos Institute (2008). *Nationale Dugs Monitor 2007*. In (http://www.trimbos.nl/~/media/Themas/7_Feiten_Cijfers_Beleid/AF0809%20NDM%20Jaarbericht%202007%20compleet%20met%20destinations.ashx), accessed 21st of November 2012. Trimbos Institute,The Netherlands Institute of Mental Health and Addiction.

United Nations Office on Drugs and Crime (2009). *World Drug Report 2009*. In (http://www.unodc.org/documents/wdr/WDR_2009/WDR2009_eng_web.pdf), accessed 19th of November 2012. New York: 2009.

Vallejo, M. A., Jordan, C. M., Diaz, M. I., Comeche, M. I. & Ortega, J. (2007). Psychological assessment via the internet: a reliability and validity study of online (vs paper-and-pencil) versions of the General Health Questionnaire-28 (GHQ-28) and the Symptoms Check-List-90-Revised (SCL-90-R). *J. Med. Internet. Res.* **9**, e2.

van Gastel, W. A., MacCabe, J. H., Vreeker, A., Tempelaar, W., Kahn, R. S. & Boks, M. P. M. (2012a). Cigarette Smoking is equally strongly associated with Psychotic-like Experiences as Cannabis Use. *Under review*.

van Gastel, W. A., Tempelaar, W., Bun, C., Schubart, C. S., Kahn, R. S., Plevier, C. & Boks, M. P. M. (2012b). Cannabis Use as an Indicator of Risk for Mental Health Problems in Adolescents. *Psychol. Med.* **3**, 1-8.

van Gastel, W. A., Wigman, J. T., Monshouwer, K., Kahn, R. S., van Os, J., Boks, M. P. & Vollebergh, W. A. (2012c). Cannabis use and subclinical positive psychotic experiences in early adolescence: findings from a Dutch survey. *Addiction* **107**, 381-387.

van Laar, W. (2011). *Nationale Drug Monitor 2011*. In (http://www.trimbos.nl/webwinkel/productoverzicht-webwinkel/feiten---cijfers---beleid/af/~/media/files/inkijkexemplaren/af1154%20 nationale%20drug%20monitor%20jaarbericht%202011_web%20lr.ashx), accessed 19th November 2012. Trimbos Institute: Utrecht.

van Leeuwen, A. P., Verhulst, F. C., Reijneveld, S. A., Vollebergh, W. A., Ormel, J. & Huizink, A. C. (2011). Can the gateway hypothesis, the common liability model and/or, the route of administration model predict initiation of cannabis use during adolescence? A survival analysis--the TRAILS study. *J. Adolesc. Health* **48**, 73-78.

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P. & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol. Med.* **39**, 179-195.

van Os, J., Bak, M., Hanssen, M., Bijl, R. V., De Graaf R. & Verdoux, H. (2002). Cannabis use and psychosis: a longitudinal population-based study. *Am. J. Epidemiol.* **156**, 319-327.

van Os, J., Hanssen, M., De Graaf, R. & Vollebergh, W. (2002b). Does the urban environment independently increase the risk for both negative and positive features of psychosis? *Soc. Psychiatry Psychiatr. Epidemiol.* **37**, 460-464.

van Os, J. & Kapur, S. (2009). Schizophrenia. *Lancet* **374**, 635-645.

van Os, J., Kenis, G. & Rutten, B. P. (2010). The environment and schizophrenia. *Nature* **468**, 203-212.

van Os, J., Verkooyen, R., Hendriks, M., Henquet, C., Bak, M., Marcelis, M., Delespaul, P., Krabbendam, L. & Myin-Germeys, I. (2008). [A psychosis proneness-persistence-impairment model of psychotic disorders]. *Tijdschr. Psychiatr.* **50 Spec no.**, 77-83.

van Winkel, R., van Beveren, N. J. & Simons, C. (2011). AKT1 moderation of cannabis-induced cognitive alterations in psychotic disorder. *Neuropsychopharmacology* **36**, 2529-2537.

Veling, W. & Susser, E. (2011). Migration and psychotic disorders. *Expert. Rev. Neurother.* **11**, 65-76.

Vendrig, L., Derksen, J. & de Mey, H. (2000). Veranderingen in het psychisch welbevinden van de nederlandse bevolking. *Gedrag en Gezondheid* **28**, 47-53.

Verdoux, H., Sorbara, F., Gindre, C., Swendsen, J. D. & van Os, J. (2003). Cannabis use and dimensions of psychosis in a nonclinical population of female subjects. *Schizophr. Res.* **59**, 77-84.

Vleeschouwer, M., Schubart, C. D., Henquet, C., Myin-Germeys, I., van Gastel, W. A., Hillegers, M. H. J., Boks, M. P. M., van Os, J. & Derks, E. M. (2012). Does assessment type matter? A Measurement Invariance analysis of online and paper and pencil assessment of the Community Assessment of Psychic Experiences (CAPE). *submitted manuscript*.

von Sydow K., Lieb, R., Pfister, H., Hofler, M. & Wittchen, H. U. (2002). What predicts incident use of cannabis and progression to abuse and dependence? A 4-year prospective examination of risk factors in a community sample of adolescents and young adults. *Drug Alcohol Depend.* **68**, 49-64.

Weiser, M., Reichenberg, A., Grotto, I., Yasvitzky, R., Rabinowitz, J., Lubin, G., Nahon, D., Knobler, H. Y. & Davidson, M. (2004). Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. *Am. J. Psychiatry* **161**, 1219-1223.

Welham, J., Scott, J., Williams, G., Najman, J., Bor, W., O'Callaghan, M. & McGrath, J. (2009). Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: a 21-year birth cohort study. *Psychol. Med.* **39**, 625-634.

Werb, D., Fischer, B. & Wood, E. (2010). Cannabis policy: time to move beyond the psychosis debate. *Int. J. Drug Policy* **21**, 261-264.

Widenfelt, B., Goedhart, A., Treffers, P. & Goodman, R. (2003). Dutch version of the Strengths and Difficulties Questionnaire (SDQ). *European Child & Adolescent Psychiatry* **12**, 281-289.

Wigman, J. T., van Winkel R., Raaijmakers, Q. A., Ormel, J., Verhulst, F. C., Reijneveld, S. A., van, Os. J. & Vollebergh, W. A. (2011). Evidence for a persistent, environment-dependent and deteriorating subtype of subclinical psychotic experiences: a 6-year longitudinal general population study. *Psychol. Med.* **41**, 2317-2329.

Wigman, J. T., Vollebergh, W. A., Raaijmakers, Q. A., Iedema, J., van Dorsselaer S., Ormel, J., Verhulst, F. C. & van Os, J. (2009). The Structure of The Extended Psychosis Phenotype in Early Adolescence--A Cross-sample Replication. *Schizophr. Bull. Epub Dec 31 2009, published on paper July 2011* ***37****, 850-860.*

Wignall, N. D. & de, Wit, H. (2011). Effects of nicotine on attention and inhibitory control in healthy nonsmokers. *Exp. Clin. Psychopharmacol.* **19**, 183-191.

Wiles, N. J., Zammit, S., Bebbington, P., Singleton, N., Meltzer, H. & Lewis, G. (2006). Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British National Psychiatric Morbidity Survey. *Br. J. Psychiatry* **188**, 519-526.

Wilson, R. I. & Nicoll, R. A. (2002). Endocannabinoid signaling in the brain. *Science* **296**, 678-682.

Wittchen, H. U., Frohlich, C., Behrendt, S., Gunther, A., Rehm, J., Zimmermann, P., Lieb, R. & Perkonigg, A. (2007). Cannabis use and cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal community study in adolescents. *Drug Alcohol Depend.* **88 Suppl 1**, S60-S70.

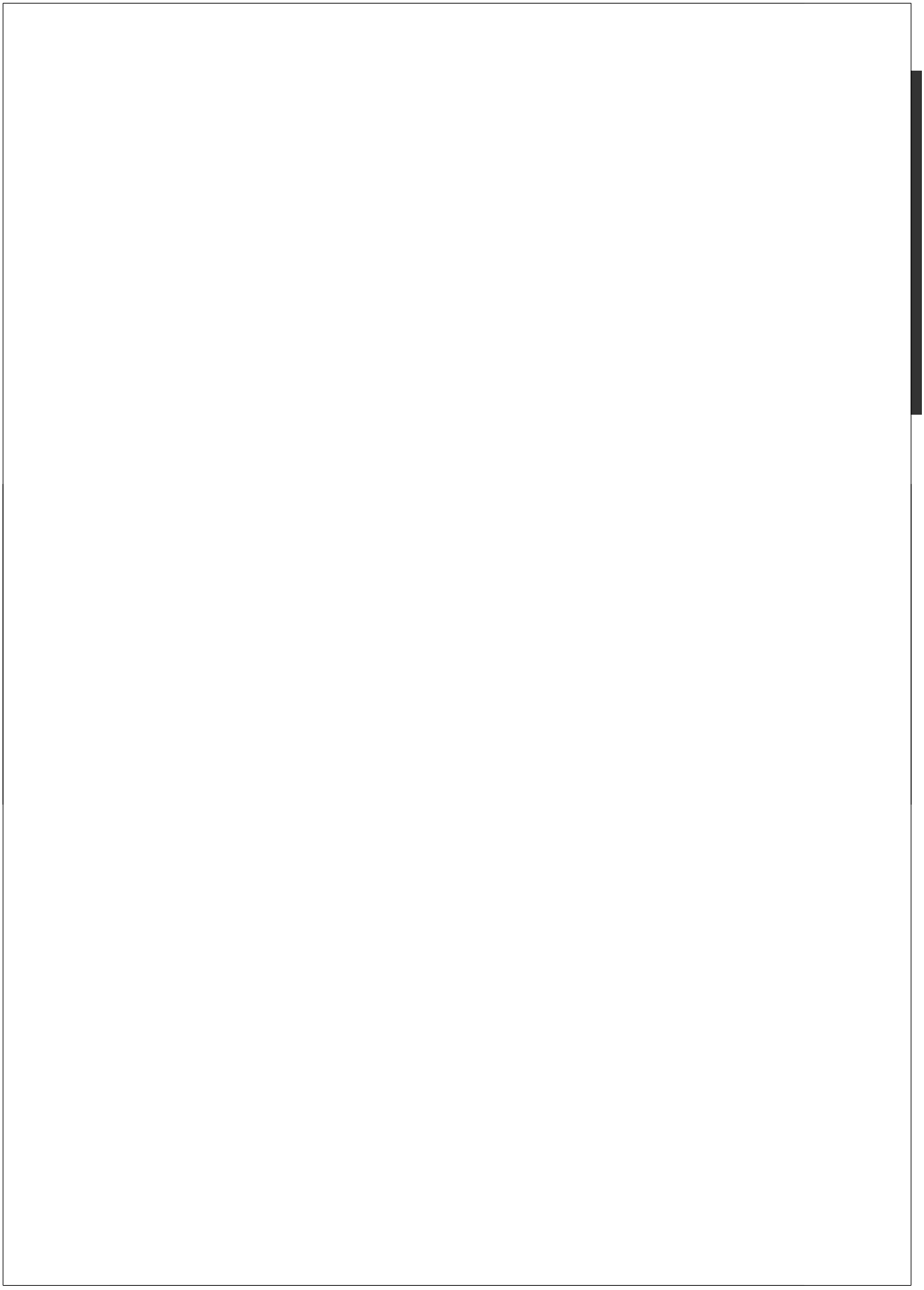
Yung, A. R., Nelson, B., Baker, K., Buckby, J. A., Baksheev, G. & Cosgrave, E. M. (2009). Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia. *Aust. N. Z. J. Psychiatry* **43**, 118-128.

Yung, A. R., Phillips, L. J., Yuen, H. P., Francey, S. M., McFarlane, C. A., Hallgren, M. & McGorry, P. D. (2003). Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophr. Res.* **60**, 21-32.

Zaldivar, B. F., Garcia Montes, J. M., Flores, C. P., Sanchez, S. F., Lopez, R. F. & Molina, M. A. (2009). Validity of the self-report on drug use by university students: correspondence between self-reported use and use detected in urine. *Psicothema.* **21**, 213-219.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I. & Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ* **325**, 1199.

Ziedonis, D., Hitsman, B., Beckham, J. C., Zvolensky, M., Adler, L. E., Udrain-McGovern, J., Breslau, N., Brown, R. A., George, T. P., Williams, J., Calhoun, P. S. & Riley, W. T. (2008). Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine. Tob. Res.* **10**, 1691-1715.



10 Dankwoord

Na bijna 10 jaar Uithof en precies 6 jaar UMC is het tijd voor een nieuwe fietsroute… Mijn tijd in het UMC is leerzaam, intensief en ook Heel Erg Gezellig geweest. Iedereen die daaraan heeft bijgedragen wil ik hartelijk bedanken!

Allereerst alle **proefpersonen** die mee hebben gedaan aan de CannabisQuest. Het beantwoorden van die eindeloze vragen, het doneren van jullie bloed, het retourneren van extra formulieren… zonder jullie deelname was dit proefschrift niet mogelijk geweest!

Marco, mijn co-promotor. Bedankt voor het vertrouwen dat je in mij gesteld hebt, ik geloof dat je tot op de dag van vandaag geen CV van mij gezien hebt… Ik heb veel geleerd van onze samenwerking: professioneel, inhoudelijk en persoonlijk. De vrijheid die je me (meestal ;) gaf heeft me goed gedaan. Ik ben trots op het werk dat we samen hebben geleverd, juist omdat het niet altijd even makkelijk ging.

René, mijn promotor. Hoe lang ik ook op een overzicht of paper had gezeten, je haalde er altijd direct wel iets uit wat niet klopte of beter kon. Je kritische houding en overzicht van het veld hebben me erg geholpen.

De leescommissie: Prof. dr. **Niek de Wit**, Prof.dr. **Guus Schrijvers**, Prof.dr. **Inez Myin-Germeys**, prof.dr **Frank Koerselman** en Prof.dr. **Wim van den Brink**. Hartelijk dank voor het kritische lezen van mijn manuscript en het zitting nemen in mijn corona.

Mijn paranimfen, Kirstin en Kelly. **Kelly**, groen als gras kwam ik bij je te werken. Vers terug uit Azië was het hard werken om me thuis te voelen in ons grauwe kikkerland, en dan ook nog in een grijs gebouw waar de ramen niet eens open konden… Met jou op de kamer was het echter een feest! Ook al was je mijn begeleider, je hebt me van begin af aan als gelijkwaardige benaderd, tegen de medische mores in. Je bent een bijzondere vriendin, door dik en dun, en ik mis je als een malle daar in Cambridge!

Kirstin, het kostte me even wat overredingskracht maar wat was het een goede beslissing om samen op een kamer te gaan zitten! Naast het vele werk dat je hebt verzet voor de CannabisQuest waarvoor ik je natuurlijk wil bedanken, ben je vooral een goede vriendin van me geworden. Zeker na de *magic week* in Londen kon het niet meer stuk :). Ik heb enorm veel steun aan je gehad tijdens het laatste jaar van mijn promotie en ik zal ons zwijgzame headbangen achter de computer en onze latte macchiato's bij **Jurjen en zijn collega's van Micaffé** missen (zonder de ladingen caffeïne die ik bij jullie naar binnen heb gegoten was ik hier niet toe in staat geweest ;). Gelukkig hebben ze in Amsterdam ook koffie!

Remko! Soms zwijgzaam, dan weer een ware spraakwaterval… Het was me een waar genoegen om je kamergenoot te zijn de afgelopen maanden. Ook daarvoor al hebben we ellenlange gesprekken gevoerd, in het park, de Brink of bij de achteringang. In het begin zorgde je er vakkundig voor dat ze over allesbehalve jou gingen, ik ben blij dat dat inmiddels veranderd is.

Chris, het vele en grondige werk dat jij hebt verricht aan het opzetten van de CannabisQuest heeft mij veel gebracht. Het moet niet makkelijk geweest zijn om dat 'kindje' met iemand te moeten delen… Samen hebben we uiteindelijk toch een mooi onderzoek draaiende weten te houden, en er mooie artikelen over geschreven!

Het CannabisQuest onderzoek heeft voor een groot deel gedraaid op de grote inzet van onze stagiaires en onderzoeksassistenten. **Sterre**, **Eveline, Marthe**, **Esther, Jeroen** en **Annabel**: bedankt voor jullie niet aflatende inzet voor het CannabisQuest onderzoek! Datzelfde geldt voor alle stagiairs die ons geholpen hebben bij het includeren van proefpersonen, het bijhouden en analyseren van alle gegevens en niet te vergeten de lol die we hebben getrapt op de onderzoekskamer, tijdens lunches en tijdens uitstapjes en pizza-avonden! Bedankt: **Alain**, **Alfred**, **Anne-Marije, Ariel, Benjamin**, **Céline**, **Christine**, **David**, **Eline**, **Eline van O**, **Fatih**, **Iris**, **Jasper**, **Jeroen B**, **Jeroen S**, **Jette**, **Joanne**, **Julie**, **Karin**, **Klaudia**, **Lander** (ik wacht nog steeds op de CannabisQuestsong…), **Laura**, **Laura S**, **Leontien**, **Lina**, **Liselotte, Marieke M**, **Marieke W**, **Marjet**, **Marloes**, **Martin**, **Mieke**, **Mirte**, **Muriël**, **Paula**, **Rogier**, **Sabine**, **Sanne**, **Sven** en **Tiny**.

Dear **James**, I enjoyed working with you at the IoP a lot! I think the line on your coffeemug 'Keep calm and carry on' characterizes you well. This attitude was a great remedy for the sometimes seemingly endless statistical analyses. I am honored to have you over for my defence! **Frankie**, thanks to you and your lovely guesthouse I felt at home right away! Thank you **Jiadi, Viviana, Feng, Maura, Asif, Cédric, Paula, Giada and all the others**. We'll meet again!

Hanneke, ik vond het geweldig om samen aan een paper te werken! Je bent snel, helder, efficient en toch heel gezellig, best een knappe combinatie :). Volgens mij ga je een gouden toekomst tegemoet! Ik hoop nog eens met je samen te werken, en als dat niet lukt houden we het gewoon bij onze koffiedates. Ook **Wilma** en **Karin**: bedankt voor de prettige samenwerking!

In Maastricht wil ik graag **Cécile** en **Jim** bedanken voor de prettige samenwerking. **Hamid, Paul** en **Dick** van de GGD regio Utrecht, bedankt voor de leuke samenwerking! Door met

jullie op pad te gaan weet ik nu veel beter waar ik over schrijf. **Paula** van Victas/Centrum Maliebaan, bedankt dat ik met je mee mocht op veldwerk! **Clothilde, Carolien, Nelleke** en **Afke** van GGD Midden Nederland, bedankt voor de goede samenwerking! Verder wil ik **Sander** en **Raymond** van het Trimbos Instituut bedanken, en **Toine** van de UU.

Roelof van Ragfijn: bedankt voor je inzet voor de CannabisQuest onderzoekssite! **Ilse, Jelle, Patricia** en **Christy** van Ipskamp, bedankt voor jullie hulp om mijn manuscript tot een boekje te maken.

Iris: door jou ben ik binnengekomen op de afdeling. Ik wil je ook bedanken voor de kansen die je me hebt gegeven om als onderzoeksassistent bij het Spectrumonderzoek te werken, als therapeut op de Stemmenpoli en als auteur.

Speciale dank aan mijn andere collega's bij de stemmenpoli, ik heb met veel plezier met jullie samengewerkt! **Yvonne**, **Julia**, **Steven**, **Christine**, **Esther**, **Annet**, **Sanne, Lot** en **Vivian**. **Rob**, hartelijk dank voor de waardevolle supervisie en intervisie die je voor ons verzorgde. Ook **Carlos** en **Tonnie**: bedankt voor de inspirerende intervisiebijeenkomsten!

Ron: ik heb veel van je geleerd en ik kijk met plezier terug op onze samenwerking!

Alle andere collega's die voor goede 'secundaire arbeidsvoorwaarden' hebben gezorgd, in Zandvoort, Florence, tijdens de wegbezuinigde vrijdagmiddagborrel en gewoon op de afdeling: de oude Spectrumgroep (wat heb ik met jullie gelachen!), fervente borrelaars, gangkletsers, theeleuten, medecursisten en kritische denkers: **Antoin**, **Thomas**, **Marleen**, **Anne**, **Mirjam**, **Tjerk**, **Cé**, **Bas**, **Bram**, **Mariët**, **Sanne V**, **Sanne K**, **Jaap**, **Elemi**, **Christiaan S, Christiaan V**, **Steven**, **Annet**, **Marieke**, **Patrick**, **Matthijs B**, **Mireille, Leo, Suzanne, Maarten-Jan, de jongens van de IT, Emmy, Elly, Tjen, Linda, Tania, Alette, Karin, Maria** en **Eske.** In het bijzonder wil ik **Annabel**, **Wanda**, **Lucija** en **Esther** bedanken: van begin af aan waren jullie meer dan gewoon collega's! De koffiedates houden we er gewoon in :)

Kees en **Margreet**, pap en mam. Dit proefschrift is aan jullie opgedragen. Zonder jullie warmte, vertrouwen, steun en ruimte had ik dit niet voor elkaar kunnen krijgen. Jullie zijn er altijd voor me, met raad en daad.

Bernard, lieve grote broer! We doen ons eigen ding en zoeken elkaar altijd weer op. Ik ben gek op onze broer-zusdates en vind het geweldig om te horen met wat voor futuristisch project je nu weer bezig bent... Je kiest altijd mijn kant, je hebt geen idee hoe goed me dat doet. **Floor**, je bent een schat!

Oma, altijd de eerste die ik bel met een nieuwtje. Je leeft met alles mee en bent vaak beter op de hoogte dan ik. Als het me eens niet meezit spreek je me moed in, *neus in de wind...* **Opa** maakt mijn promotie niet meer mee, maar hij zit in ieder van ons.

Lieve familie, ook jullie bedankt! Jullie maken me tot wie ik ben. **Heleen, Siebe, Nina, Kees, Kaatje, Julius, Vera, Gert, Madelief, David, Hannah, Berend, Hildegard, Emiel, Elisabeth, Eloïse, Joost, Maarten, Mieke, Harry, Pieter, Esther, Simon en Janneke. Corrie, Ada, Leendert, Anneke, Myrthe, Isa, Jolijn, Pali, Beatrice, Luigi, Mario** en **tante Rita**.

Anita, **Remke** en **Robert**, inmiddels zijn jullie ook familie! Bij jullie voel ik me thuis.

Roelant en **Pien**, bedankt voor de lange gesprekken die we hebben gevoerd over de wetenschap, mijn promotie en alle andere dingen die daarbij kwamen kijken! Ik vind het heel bijzonder hoe jullie elke keer weer onvermoeid blijven doorvragen en meedenken.

Lieve **Elleke**, vriendinnetje van altijd! Ook de afgelopen jaren was je er altijd voor me. Je bent heel belangrijk voor me. **Lennert**, **Els**, **Pieter**, **Perijn** en **Marie**, ik vind het altijd heerlijk om jullie te zien! En ook de rest van het Arnhemse thuisfront: zo vaak zien we elkaar niet meer, maar ik weet dat jullie er zijn en dat doet me goed! **Floor, Paul, Inge, Klaas, Daan, Danique, Jacqueline, Michiel, Stijn, Wouter** en natuurlijk 'ome' **Theo**.

Lieve **Roos**, vlak voor het begin van mijn promotie zijn we samen op vakantie geweest naar Spanje en vlak voor het einde ervan naar Thailand. Dat tekent ook wat een bijzondere vriendin je voor me bent, met jou kan ik de wereld rond!

Arjan, jij verdient een eigen plekje in dit dankwoord. Het begin van mijn promotie heb je intensief meegemaakt. Bedankt voor alle steun die je me hebt gegeven. **Suus**, ik ben blij dat je er bent! **Marie-Louise, Hans, Marlou, Kasper, Oma Roermond, Oma Helvoirt** en de rest van de familie(s): bedankt voor de warmte waarmee jullie me altijd omringd hebben. Dat vergeet ik nooit.

Sas en **Naomi**, lieve Wassies! De eerste jaren van mijn promotie hebben we samengewoond, en ik heb ervan genoten! Jullie maakten het makkelijker voor me om weer te aarden na zo'n lange reis en waren heel fijne huisgenootjes (ook voor zo'n uithuizige sloddervos als ik :). Jullie zijn vooral heel fijne vriendinnen! We hebben al heel wat meegemaakt inmiddels, en er zal ook nog van alles op ons pad komen (zeker als Naomi naar conflictgebieden blijft trekken;).

Lieve **Bas, Meg, Coen, Di, Jos, Ben, Wessel, Sanne Boo, Sanne Bij, Michael, Jacq, Joost, Hilde, Ruud, Sander, Hanneke** en **Jornt**. We gaan inmiddels *way back* en ik voel me vereerd dat ik veel van jullie al zo lang zo dicht bij me heb. Ik heb het jullie niet makkelijk gemaakt de afgelopen jaren, maar weet dat ik gek op jullie ben! Zo'n loyale club vind je niet snel...

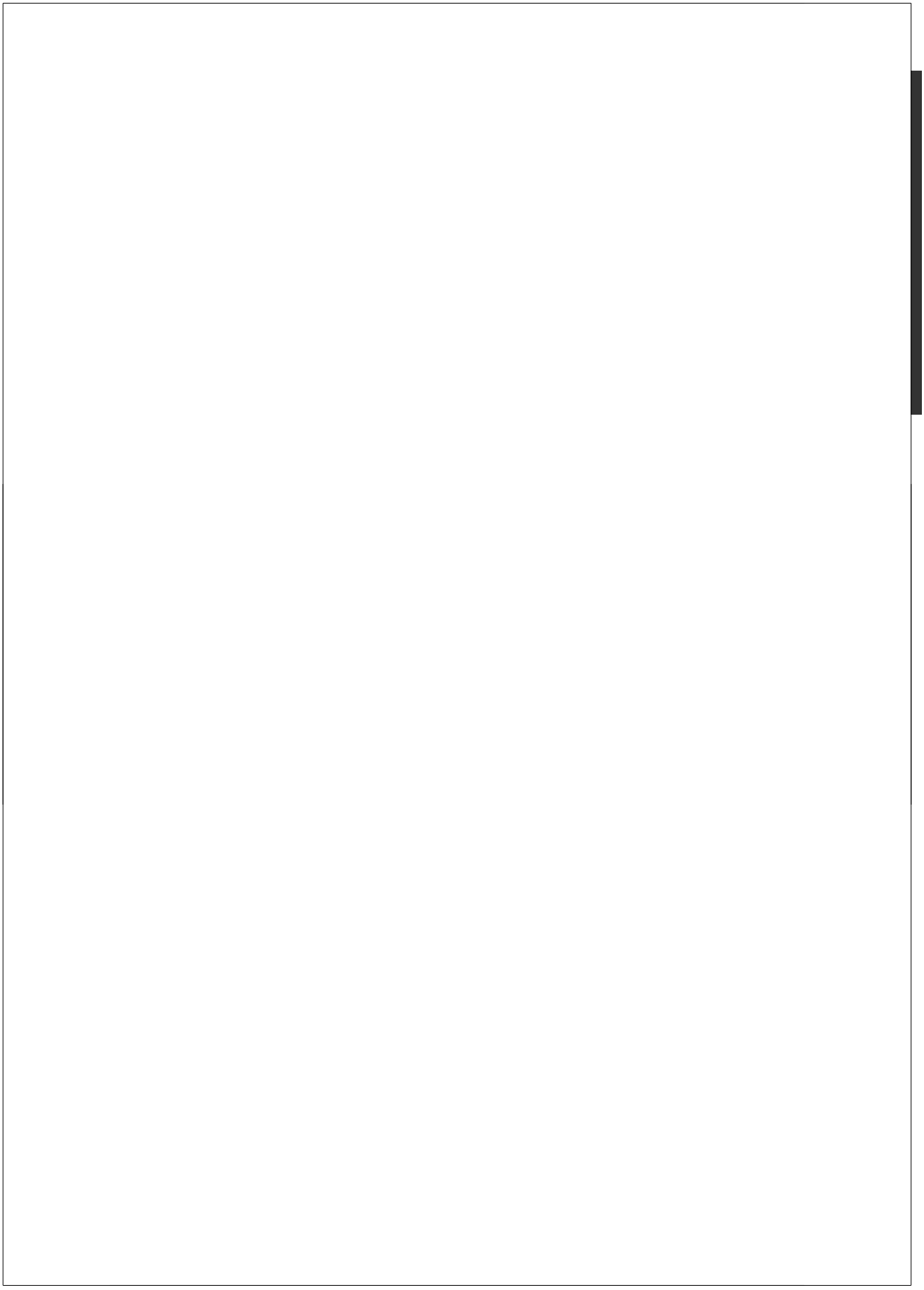
Jasper, **Daan**, **Josje** en natuurlijk kleine **Mika**, ik vind het heel gaaf dat ik jullie inmiddels ook mijn matties kan noemen :). Ik voel me altijd senang als ik bij jullie in de buurt ben. **Marc, Netty, Joeke** en **Gitte**: wanneer gaan we weer pepernoten bakken? **Jeroen**: Píjìu?

Maartje: jouw gastvrijheid en die van je familie had niet op een beter moment kunnen komen…Bia Saigon, Singha, Tiger, Heineken: met jou smaakt het allemaal goed! **Clemens:** of we nou buren worden of niet, die barbecue komt er! **Xan**: ik vind het mooi om te zien hoe jij eigen pad trekt, met lantaarn in je hand als Zarathustra of op je eigen dak in Doorn.

Ton en **Jeroen**, ik heb veel gehad aan de goede gesprekken met jullie. Bedankt!

Casper van Interfysiek, je hebt me van mijn RSI afgeholpen toen ik de hoop daarop had opgegeven... Ik heb nog dagelijks profijt van je advies en kan je niet genoeg bedanken!

Lieve **Flo**. Je kwam voorbij gefietst op een moment dat ik het niet had verwacht, en daar was je dan: niet weg te slaan uit mijn hoofd en hart. Samen stage lopen werd samen promoveren, samen reizen, samen wonen, en dat was nog maar het begin... Met jou heb ik weer ontdekt hoe het voelt om zorgeloos te zijn, misschien wel het mooiste wat je me had kunnen geven. Ik vind je gaaf!



11

List of publications

JOURNAL ARTICLES

van Gastel, W.A., MacCabe, J.H., Schubart, C.D., Vreeker, A., Tempelaar, W., Kahn, R.S., Boks, M.P.M. (2013). Cigarette smoking and cannabis use are equally strongly associated with psychotic-like experiences: a cross-sectional study in 1,929 young adults. *Psychological Medicine.* **18**, 1-9.

Vreeker, A., Schubart, C.D., **van Gastel, W.A.**, Kahn, R.S., Boks, M.P.M. (2013). Advanced paternal age and the vulnerability to subclinical psychotic experiences. *Schizophrenia Research.* **143**, 74–76.

van Gastel, W.A., Tempelaar, W., Bun, C., Schubart, C.S., Kahn, R.S., Plevier, C., Boks, M.P. (2012). Cannabis Use as an Indicator of Risk for Mental Health Problems *Psychological Medicine*. **3,** 1-8.

van Gastel, W.A., Wigman, J.T., Monshouwer, K., Kahn, R.S., van Os, J., Boks, M.P., Vollebergh, W.A. (2011). Cannabis use and subclinical positive psychotic experiences in early adolescence: findings from a Dutch survey. *Addiction*. **107**, 381-387.

Schubart, C.D., Sommer, I.E., **van Gastel, W.A.**, Goetgebuer, R.L., Kahn, R.S., Boks, M.P. (2011). Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophrenia Research.* 2011 **130**, 216-21.

Schubart, C.D., Boks, M.P., Breetvelt, E.J., **van Gastel, W.A.**, Groenwold, R.H., Ophoff, R.A., Sommer, I.E., Kahn, R.S. (2011). Association between cannabis and psychiatric hospitalization. *Acta Psychiatrica Scandinavica.* **123**, 368-75.

Diederen, K.M., Daalman, K., de Weijer, A.D., Neggers, S.F., **van Gastel, W.A.**, Blom, J.D., Kahn, R.S., Sommer, I.E. (2011). Auditory hallucinations elicit similar brain activation in psychotic and nonpsychotic individuals. *Schizophrenia Bulletin*. **38**, 1074-1082.

Schubart, C.D., **van Gastel, W.A.**, Breetvelt, E.J., Beetz, S.L., Ophoff, R.A., Sommer, I.E., Kahn, R.S., Boks, M.P. (2010). Cannabis use at a young age is associated with psychotic experiences. *Psychological Medicine.* **7**, 1-10.

SUBMITTED MANUSCRIPTS

van Gastel, W.A., MacCabe, J.H., Schubart, C.D., van Otterdijk, E., Kahn, R.S., Boks, M.P.M. (under review). Moderate cannabis use is a better indicator of poor mental health in women than in men.

Vinkers, C.H., **van Gastel, W.A.**, Schubart, C.D., van Eijk, K., Luykx, J., van Winkel, R., GROUP, Ophoff, R., Caspi, A., Boks, M.P.M. (submitted). The effect of childhood maltreatment and cannabis use on adult psychotic-like symptoms is modified by the COMT(Val/Met) polymorphism.

Schubart, C.D., **van Gastel, W.A.**, van Eijk, K., Koeleman, B., Caspi, A., Ophoff, R., Kahn, RS., Boks, M.P.M. (submitted). A P2X7 receptor polymorphism (rs 7958311) plays a key role in cannabis mediated risk of psychosis.

Schubart, C.D., de Jong, S., de Wite, L., **van Gastel, W.A.**, Helthuis, J., Koeleman, B., Ophoff, R., Kahn, R.S., Boks, M.P.M. (submitted). Genome wide expression profiling of whole blood from heavy cannabis users and controls reveals differential regulation of liprin alpha 2 (PPFIA2).

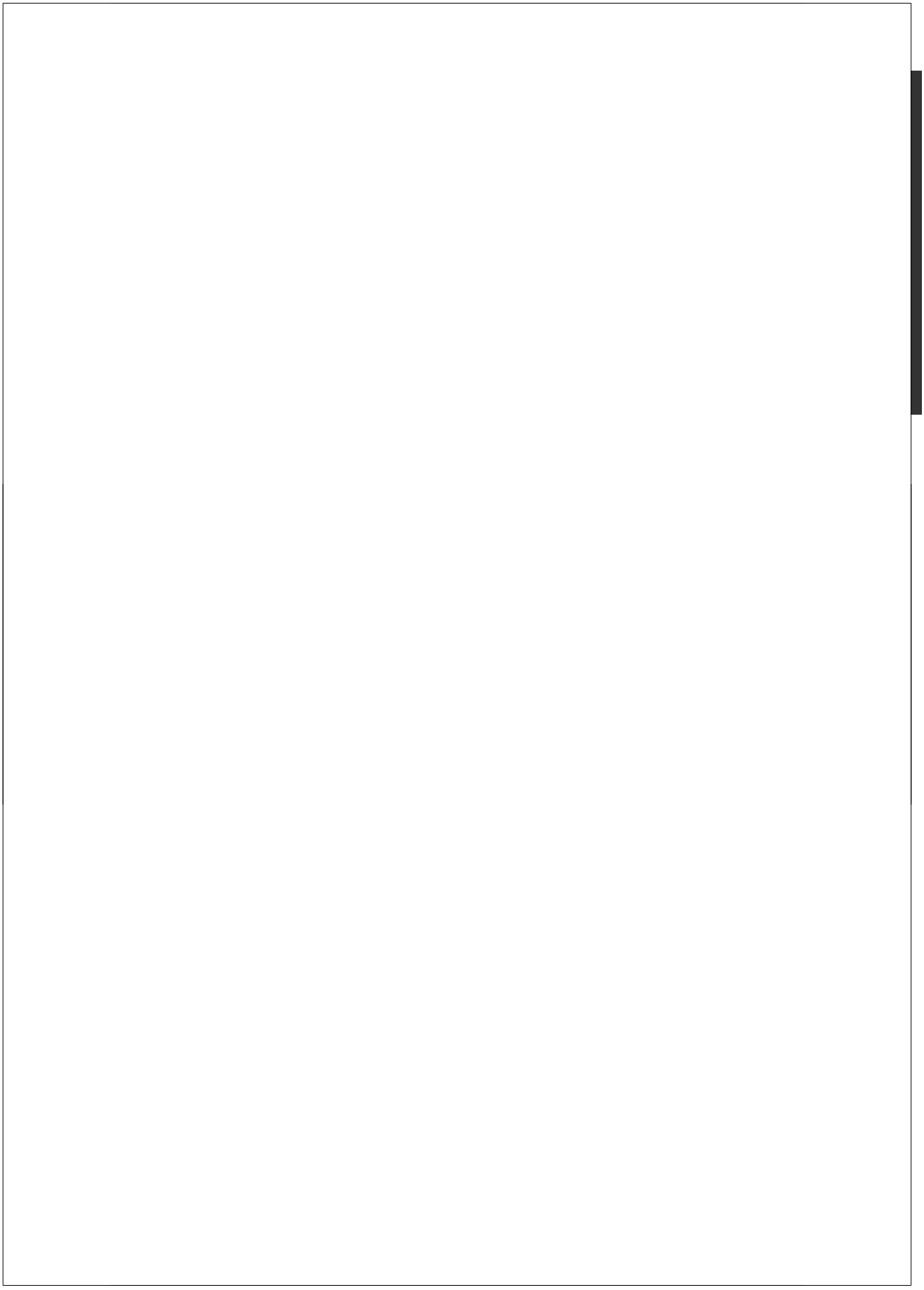
Tempelaar, W., Otjes, C., Bun, C., Plevier, C., **van Gastel, W.A.**, MacCabe, J.H., Kahn, R.S., Boks, M.P.M. (under review). Delayed school progression and mental health problems in adolescence: a population-based study in 10,803 adolescents.

Vleeschouwer, M., Schubart, C.D., Henquet, C., Myin-Germeys, I., **van Gastel, W.A.**, Hillegers, M.H.J., Boks, M.P.M., van Os, J., Derks, E.M. (under review). Does assessment type matter? A Measurement Invariance analysis of online and paper and pencil assessment of the Community Assessment of Psychic Experiences (CAPE).

BOOK CHAPTERS

Basistherapie (chapter 11) Sommer, I.C.E. & **van Gastel, W.A.**, in *Stemmen horen* by Iris Sommer, Balans uitgeverij, Amsterdam, 2011 ISBN-9789460033018

Groundwork for the treatment of voices: Introducing the Coping-With-Voices Protocol (chapter 27). **van Gastel, W.A.** & Daalman, K., in *Hallucinations. Research and Practice* edited by Blom, J.D. & Sommer, I.E.C., Springer, New York, 2012



12

Curriculum Vitae

CURRICULUM VITAE

Willemijn van Gastel was born in Arnhem, the Netherlands, on April 19th, 1985. In 2003, she finished her secondary education at the Stedelijk Gymnasium Arnhem. The same year, she started studying Psychology at Utrecht University, obtaining her Bachelor's degree in 2006. After travelling through Asia by train for eight months, she began as an intern at the Department of Psychiatry at the University Medical Center Utrecht with the research team of prof. dr. Iris Sommer. Under her supervision and that of dr. Kelly Diederen she investigated brain activity during auditory verbal hallucinations with functional MRI. Dr. Ron Hijman supervised her clinical internship. Upon obtaining a Master of Science degree in 2008, she first started as research assistant and later as PhD student with the CannabisQuest study under supervision of dr. Marco Boks and prof. dr. René Kahn. In addition to her scientific work, Willemijn has worked at the Voices Clinic Utrecht as therapist. As from April 2013, she will start clinical training as a healthcare (GZ-)psychologist at the department of Psychosomatic Medicine and Sexuology at the Academic Medical Center, Amsterdam.

CURRICULUM VITAE

Willemijn van Gastel is geboren in Arnhem, op 19 april 1985. In 2003 behaalde ze haar middelbare school diploma op het Stedelijk Gymnasium in Arnhem. In datzelfde jaar begon zij aan de studie Psychologie in Utrecht, die ze in 2006 afrondde met een Bachelordiploma. Na een treinreis door Azië van acht maanden begon zij als stagiair op de afdeling Volwassenen Psychiatrie van het Universitair Medisch Centrum Utrecht, bij de onderzoeksgroep van prof. dr. Iris Sommer. Onder haar begeleiding en die van dr. Kelly Diederen voerde ze haar afstudeeronderzoek uit naar hersenactiviteit tijdens het horen van stemmen aan de hand van functionele MRI. Dr. Ron Hijman begeleidde haar klinische stage. In 2008 behaalde ze haar Masterdiploma, waarna ze eerst als onderzoeksassisitent en aansluitend als promovendus werkte bij het CannabisQuest onderzoek, onder begeleiding van dr. Marco Boks en prof. dr. René Kahn. Naast haar wetenschappelijke werk heeft Willemijn als therapeut gewerkt bij de Stemmenpoli Utrecht. In april 2013 begint ze aan de opleiding tot gezondheidszorg(GZ-)psycholoog op de afdeling Psychosomatiek en Seksuologie in het Academisch Medisch Centrum, Amsterdam.