Cannabis use and psychosis: Past, present and future

Dr Marta Di Forti, MD, PhD
MRC Senior Clinical Fellow ,SGDP, KCL
Consultant Adult Psychiatrist, LEO team &
Lead Clinician of the Cannabis Clinic for Patents with Psychosis, South London and Maudsley NHS trust

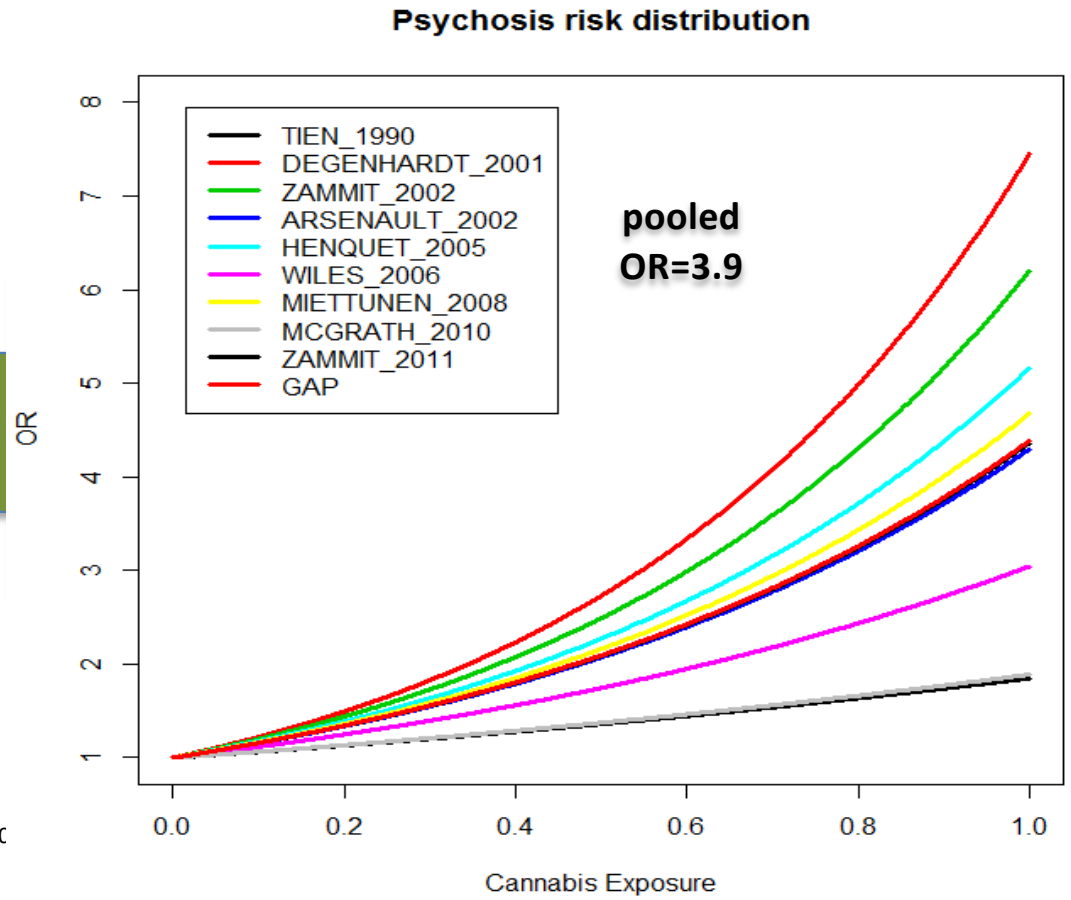
Disclosure

- I have nothing to disclose

PAST: Cannabis use and Psychotic Disorders

3 Meta-analyses

point at cannabis use as a risk factor for Psychotic Disorders



Henquet C, *et al. Schizophr Bull* 2005;**31**:608–12; Moore TH, *et al. Lancet* 2(
Marconi A, *et al. Schizophr Bull* 2016;**42**:1262–9.

Diego's paper

Psychological Medicine

cambridge.org/psm

Original Article

*See at the end of the Article for more details.

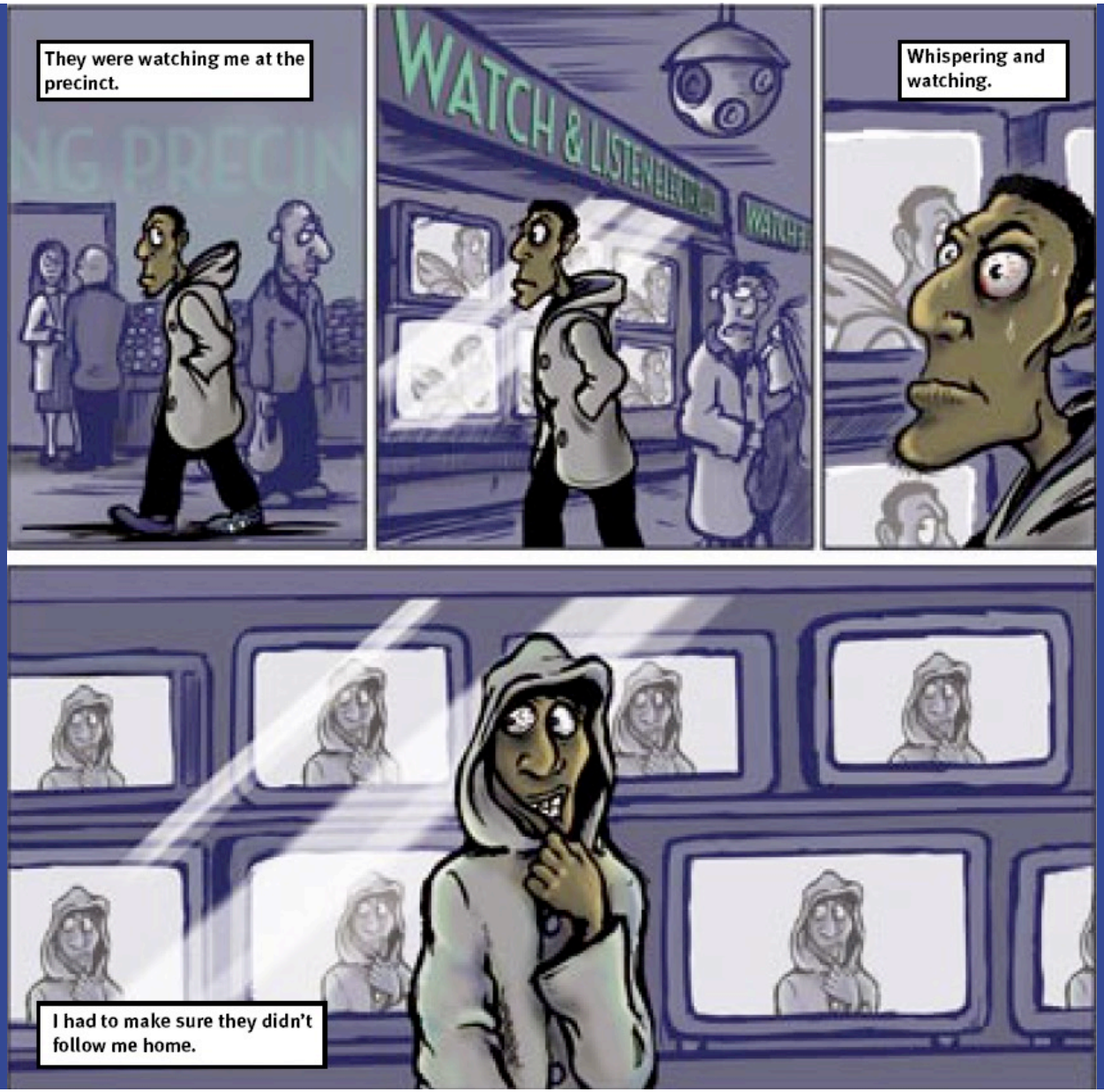
Cite this article: Quattrone D *et al* (2021). Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: the EU-GEI case–control study. *Psychological Medicine* **51**, 1329–1337. https://doi.org/10.1017/S0033291720000082

Received: 29 September 2019
Revised: 27 November 2019
Accepted: 8 January 2020
First published online: 18 March 2020

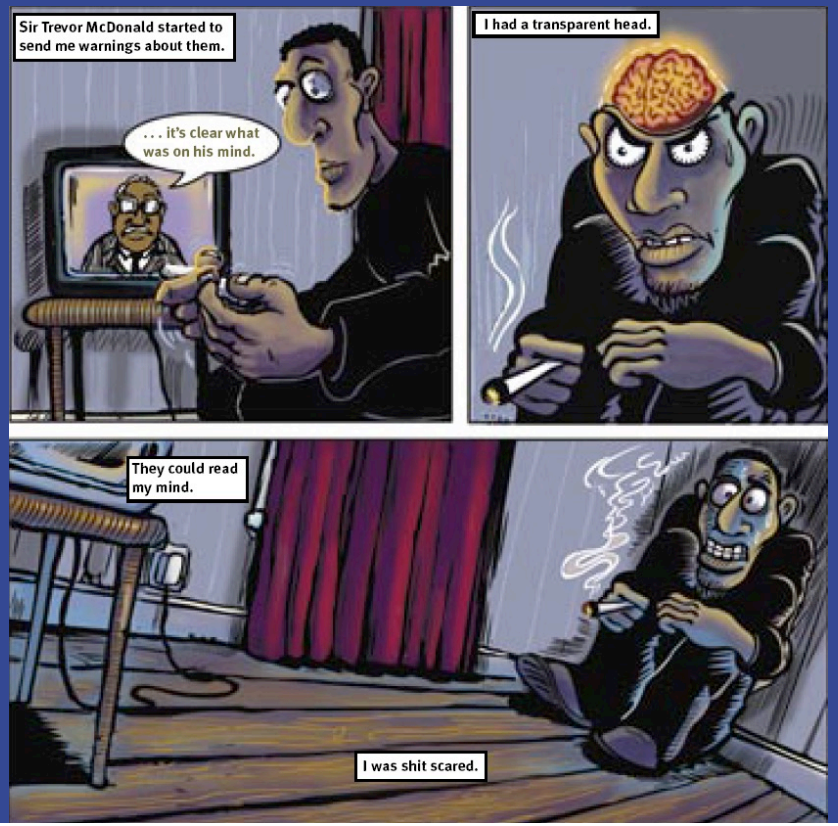
Key words:
Cannabis use; cannabis-associated psychosis; psychopathology; psychotic experiences; symptom dimensions; first episode psychosis

Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: the EU-GEI case–control study

Diego Quattrone[1,2,3], Laura Ferraro[4], Giada Tripoli[5], Caterina La Cascia[4], Harriet Quigley[5], Andrea Quattrone[6], Hannah E. Jongsma[7], Simona Del Peschio[8], Giusy Gatto[8], EU-GEI group[1,*], Charlotte Gayer-Anderson[9], Peter B. Jones[10,11], James B. Kirkbride[7], Daniele La Barbera[4], Ilaria Tarricone[12], Domenico Berardi[12], Sarah Tosato[13], Antonio Lasalvia[13], Andrei Szöke[14], Celso Arango[15], Miquel Bernardo[16], Julio Bobes[17], Cristina Marta Del Ben[18], Paulo Rossi Menezes[18], Pierre-Michel Llorca[19], Jose Luis Santos[20], Julio Sanjuán[21], Andrea Tortelli[22], Eva Velthorst[23,24], Lieuwe de Haan[23], Bart P. F. Rutten[25], Michael T. Lynskey[26], Tom P. Freeman[26,27], Pak C. Sham[28,29], Alastair G. Cardno[30], Evangelos Vassos[1], Jim van Os[25,31], Craig Morgan[9], Ulrich Reininghaus[3,9,25], Cathryn M. Lewis[1], Robin M. Murray[2,5] and Marta Di Forti[1,2]



Beliefs: we develop ”against the evidence of the contrary”
unshakable ideas, worries that others around us find bizarre or unsubstantiated
We become very suspicious and fear we are under threat or the target of a conspiracy
We fear that others can read our own thoughts and that our thoughts are no longer private



EUGEI study: 2011–2013

Incident First Episode Psychosis cases **N=1130** & population controls **N=1499**

Cambridge

London

Amsterdam + Gouda V

Paris (Val de Marne) + Clermont Ferrant

Barcelona, Madrid +3

Bologna

Palermo

Only sites with <=5% missing cannabis data

www.eu-gei.eu

Working out cannabis potency (THC %)…starting from London

Skunk – on average THC=16%
Hash THC=9–20% (CBD<3%)

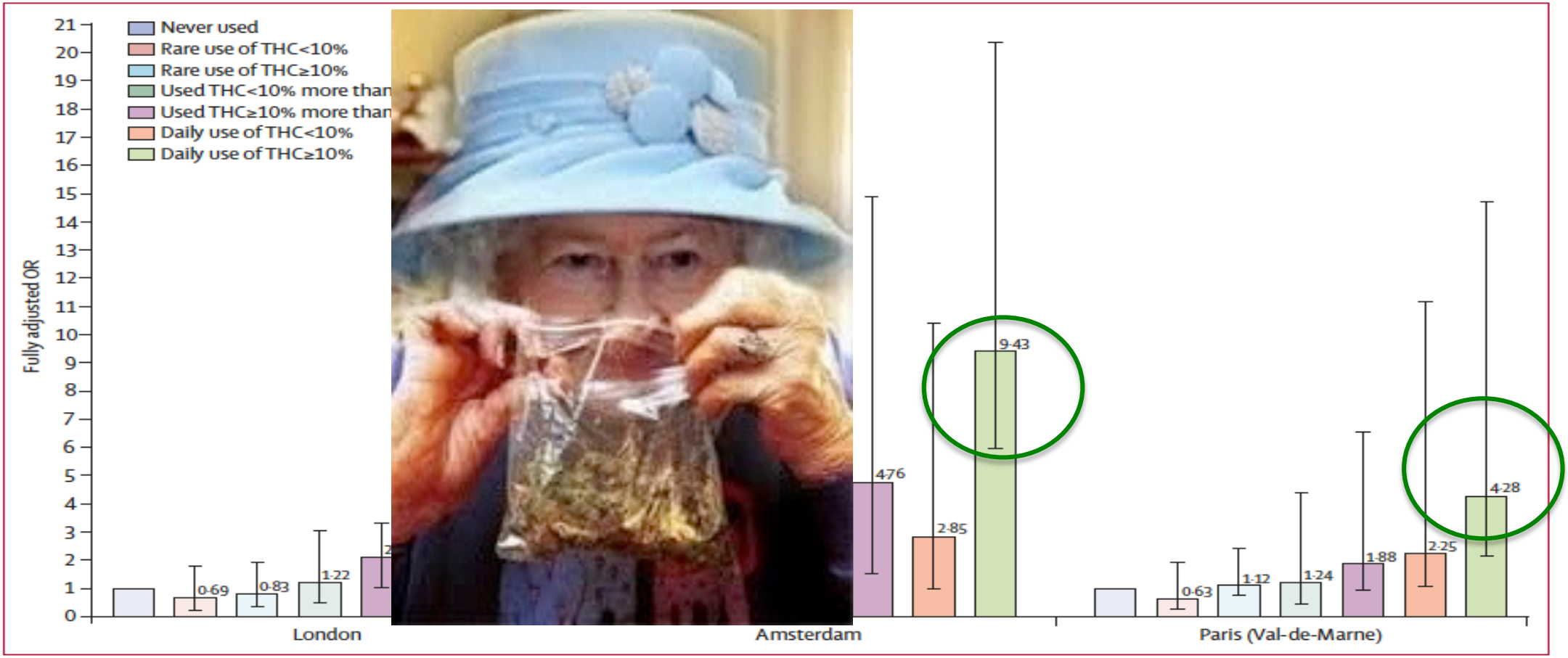
2016 Report:

European Monitoring Centre for Drugs and Drug Addiction

Low potency: THC<10%

High potency: THC=>10%

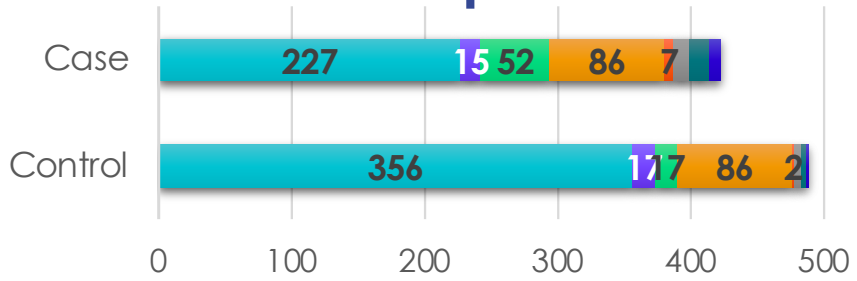
The effect of daily use of high-potency cannabis on the odds for psychotic was particularly visible in **London and Amsterdam**



*Adjusted for age, gender, ethnicity, level of Ed, employment status and other drugs (tobacco, alcohol, stimulants, Ketamine, Legal highs, Hallucinogenics).
Di Forti et al, Lancet Psych, online 2019

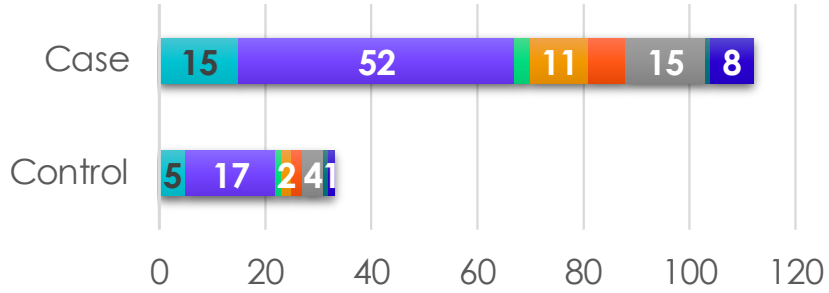
Reasons to first start using cannabis

Because of friends Friends and overlap

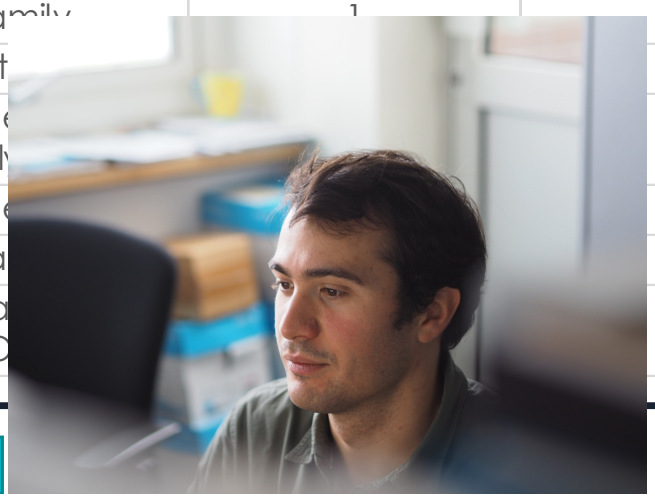


	Control	Case
Friends	356	227
Friends Family	17	15
Friends Better	17	52
Friends Other	86	86
Friends Family Better	2	7
Friends Family Other	5	12
Friends Better Other	4	15
Friends Family Better Other	1	8

To feel Better and overlap



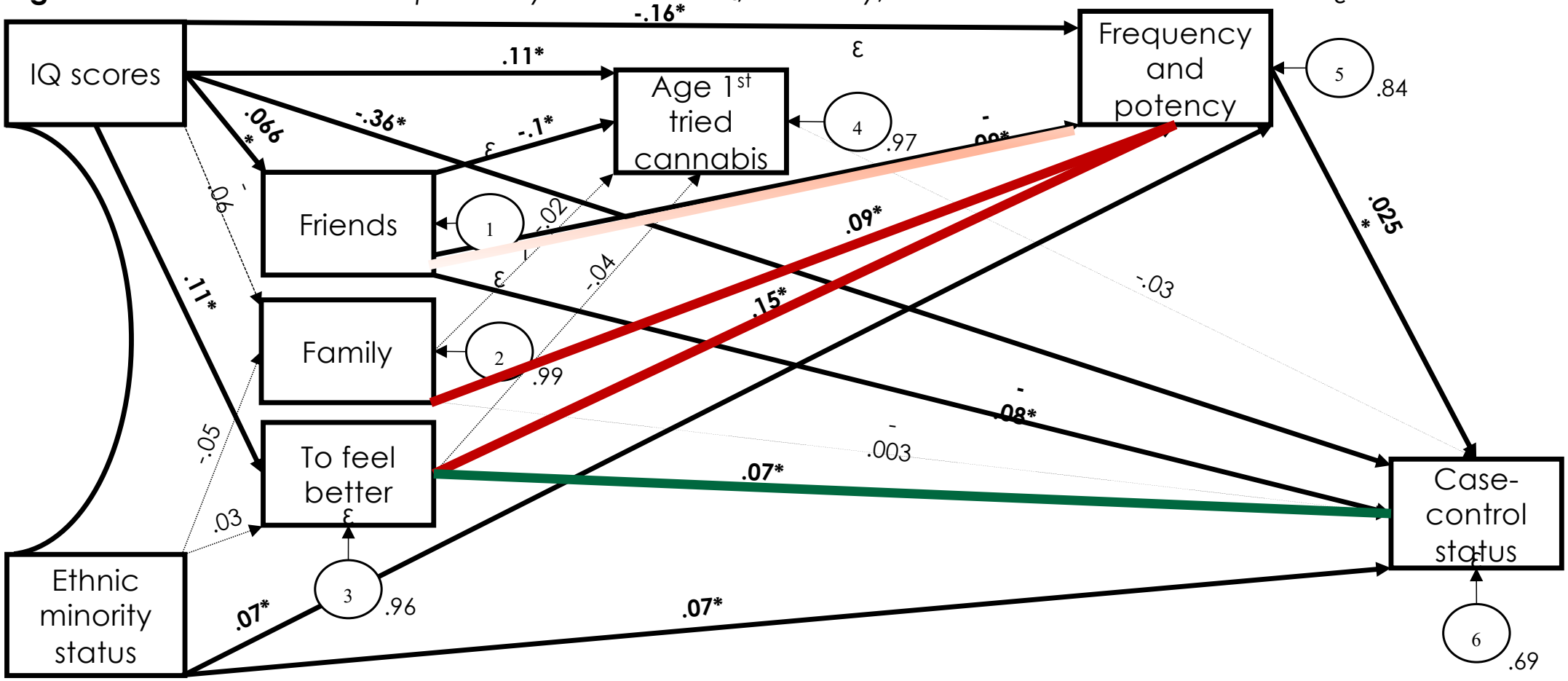
	Control	Case
Better	5	15
Better Friends	17	52
Better Family	1	3
Better Other		11
Better Friends Family		7
Better Friends		15
Better Family		1
Better Family Friends Other		8



Edoardo Spinazzola et al, 2022 under review with Addiction

What can Reason to first use cannabis tell us?

Figure 1. *Direct and indirect pathways between IQ, ethnicity, RFUC and case-control status*



The path model had a good fit to the data:
χ^2 = 12.50; p = 0,03; root mean square error of approximation (RMSEA) = 0.040; comparative fit index (CFI) = 0.99

Why does potency matter?
The prize we paid…

Courtesy of Dr Tom Freeman

UNIVERSITY OF BATH

Cannabis potency

Cannabis potency (THC)

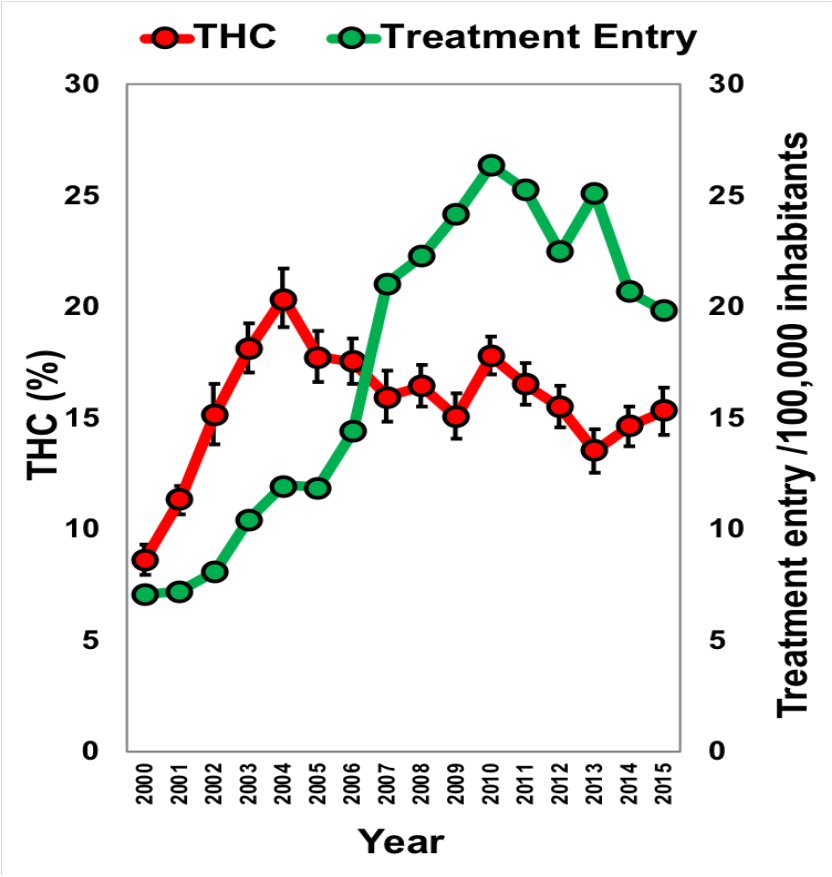
Trimbos instituut
Netherlands Institute of Mental Health and Addiction

Cannabis purchased from 'coffee shops' - Netherlands, 2000-2015

Cannabis treatment

IVZ
zicht op zorg

People entering treatment for cannabis problems - Netherlands, 2000-2015



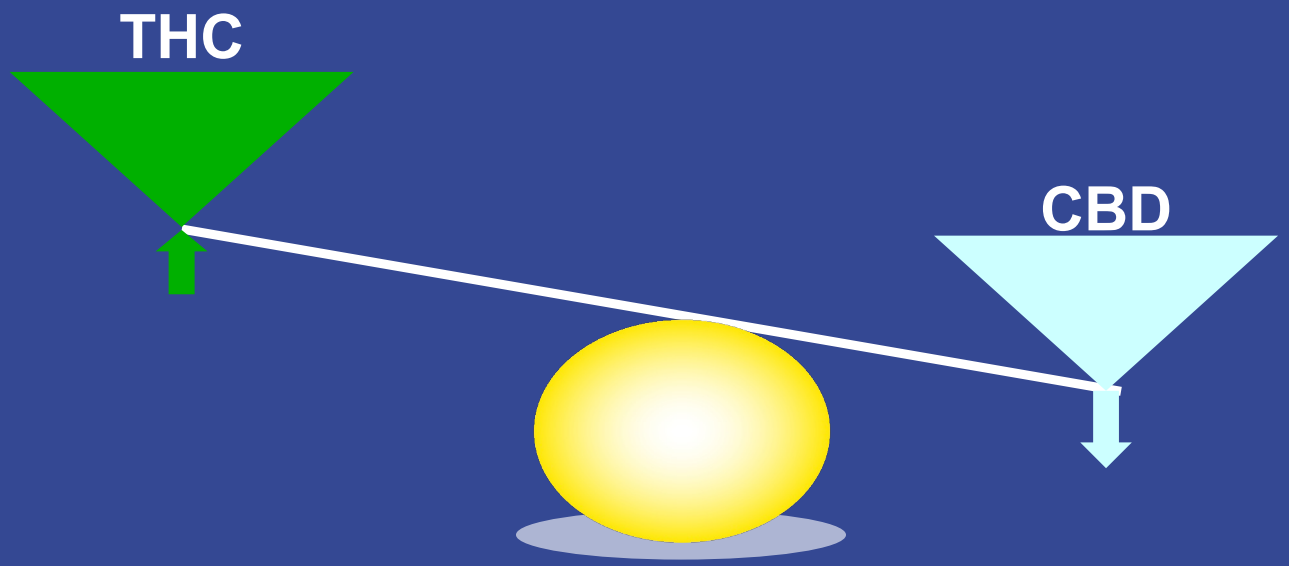
The same plant can produce high concentrations of either one or the other

THC

- Impairment of attention, memory and learning
- Hallucinations and paranoid ideas

Cannabidiol (CBD)

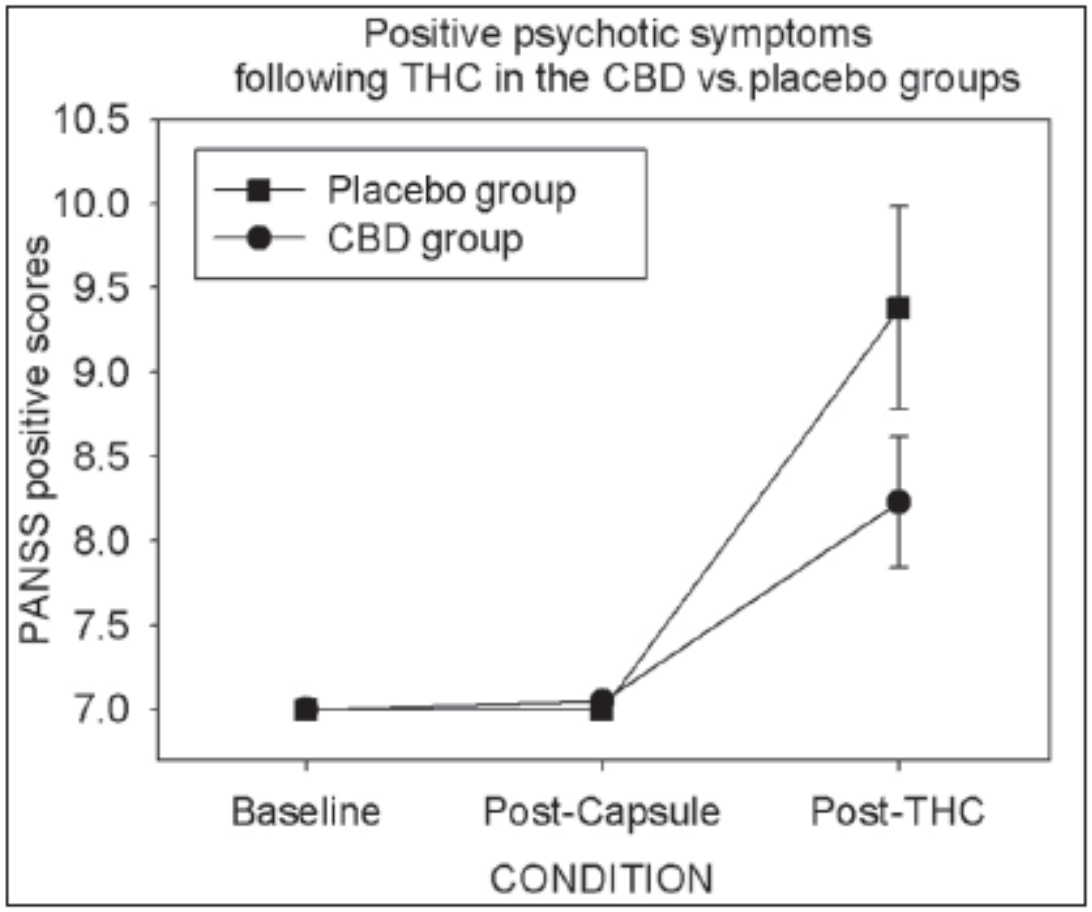
- Is not hallucinogenic
- Has anxiety relieving properties
- No adverse effect on cognition



Englund A, *et al. Lancet Psychiatry* 2017;**4**:643–8.

Psychotogenic effect of acute administration of 1.5 mg of IV Tetrahydrocannabinol (THC)

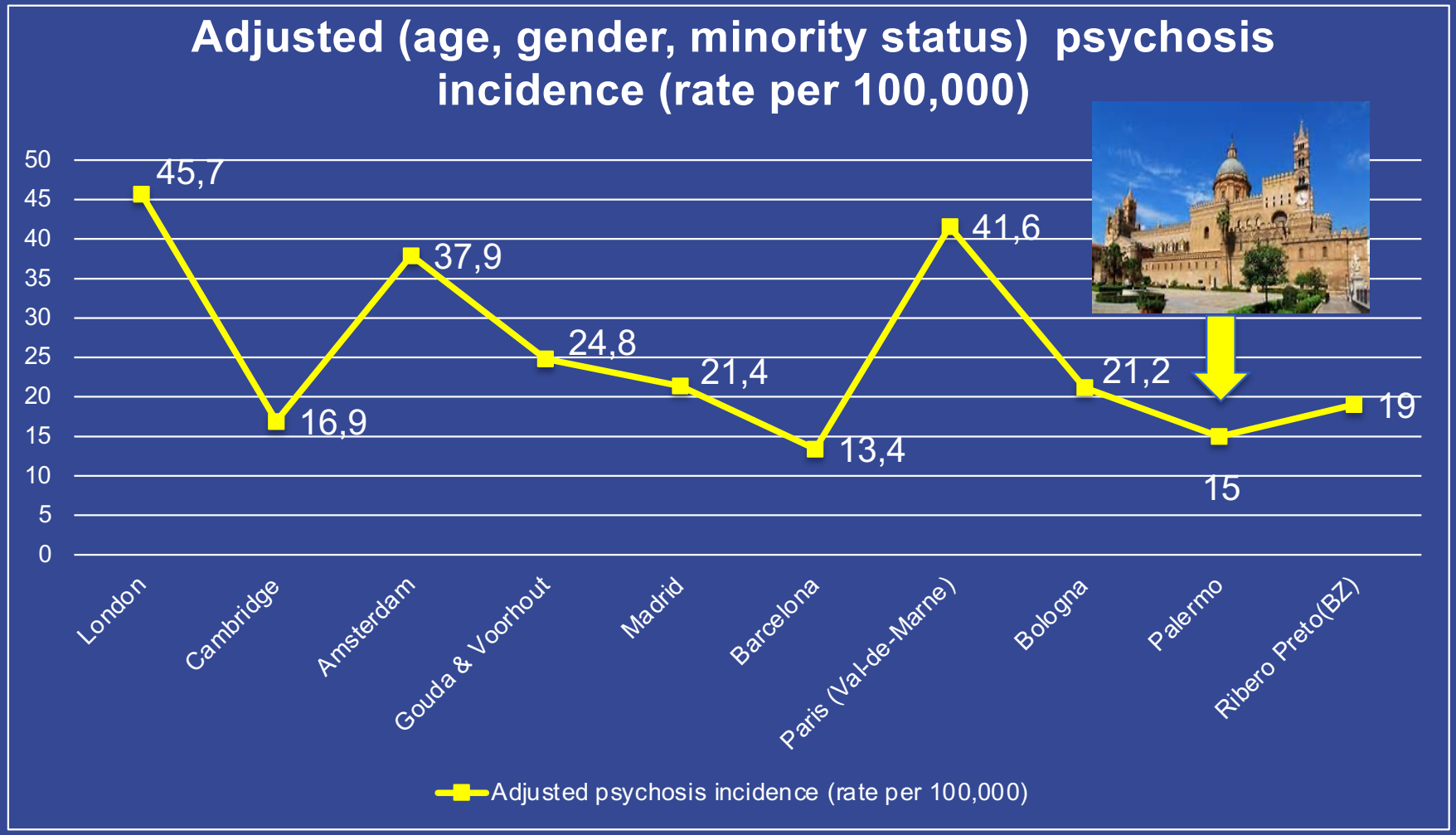
THC induces transient psychotic symptoms



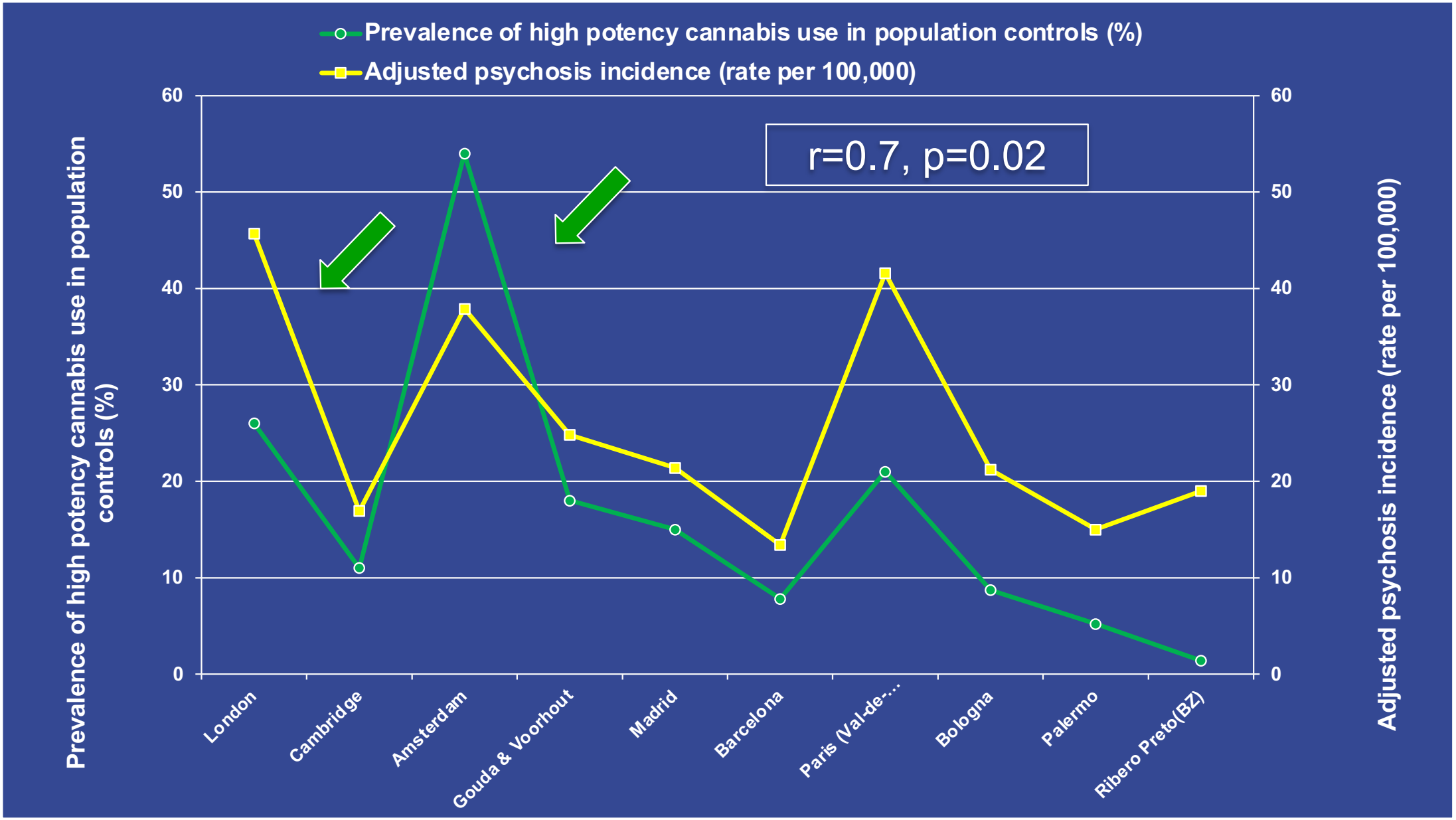
Englund A, *et al. J Psychopharmacol* 2013;**27**:19–27.

Is there a relationship between prevalence of cannabis use in the population and the incidence rates of psychosis?

Trans-European (plus Brazil)



Jongsma HE, *et al. JAMA Psychiatry* 2018;**75**:36–46.


Prevalence of high potency cannabis use in population controls (%)
Adjusted psychosis incidence (rate per 100,000)
r=0.7, p=0.02
Prevalence of high potency cannabis use in population controls (%)
Adjusted psychosis incidence (rate per 100,000)
60
50
40
30
20
10
0
London
Cambridge
Amsterdam
Gouda & Voorhout
Madrid
Barcelona
Paris (Val-de-...
Bologna
Palermo
Ribero Preto(BZ)

Population Attributable Fraction (PAF)

High Potency use	Adj OR	% FEP	PAF
Whole sample	1.6 (1.2–2.2)	35.1%	12.2% (3.0–16.1%)
London	2.4 (1.4–4.0)	51.5%	30.3% (15.2–40.0%)
Amsterdam	3.4 (1.5–7.7)	69.6%	50.3% (27.4–66.0%)
Paris	2.1 (0.8–3.6)	35.9%	**18.9%** (14.6–36.0%)

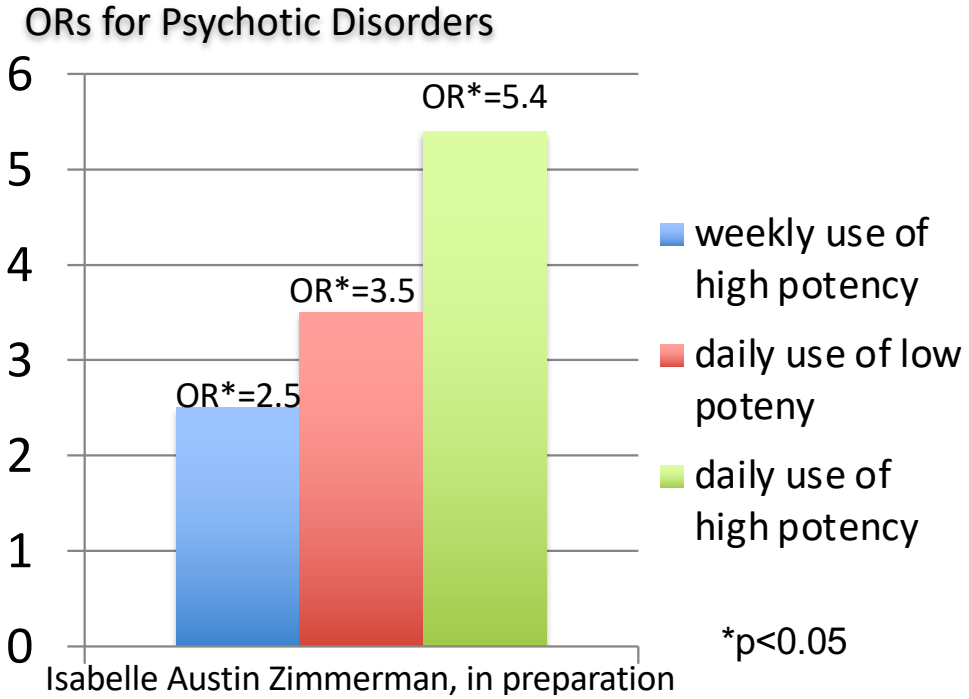
Di Forti et al, Lancet Psychiatry, online 2019

FAQs-criticism

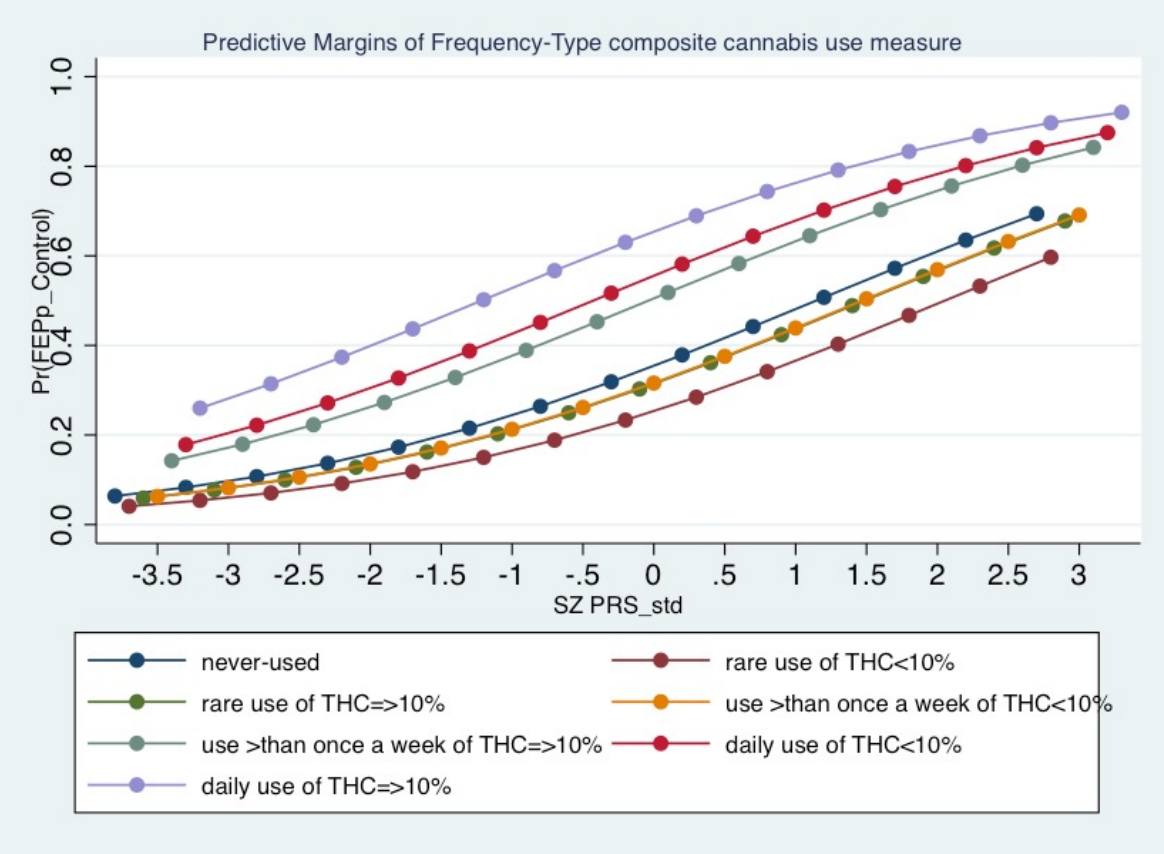
1)Genetic dispute

Is this all explained by SCZ genes predisposing to cannabis use :
NO

Even after controlling for the effect of Schizophrenia genes (SZ Polygenic risk scores) the following patterns of cannabis use increased the risk (OR) for Psychotic disorder:



Combined effect of SZ Genes (PRS) and Cannabis use



What do we know from genetic studies?

- Genetic overlap between lt-CU and CUD but different genetic underpinnings
- Genetic overlap/correlation between lt-CU, CUD and SCZ
- LCV findings suggest horizontal pleiotropy (genetic variants directly contributing to both CUD risk and SCZ risk) rather then vertical pleiotropy (genetic variants that contribute to CUD liability indirectly contributing to SCZ via a causal relationship between CUD itself and SCZ risk
- Univariate MR : mixed findings
- Johnson et al MVMR : causal relationship between CUD and SCZ

Gillepsie and Kendler, JAMA Psych, 2020:

1. CU-SCZ is entirely causal 2. CU-SCZ is partly causal and partly confounded by genetic/familial effects and/or reverse causation, or 3. CU-SCZ is entirely noncausal

One suggestion : Examine changes in incidence rates of schizophrenia in states with a rise in cannabis consumption associated with decriminalization

WILEY

Psychotic disorders hospitalizations associated with cannabis abuse or dependence: A nationwide big data analysis

Manuel Gonçalve

Cannabis was decriminalised

TABLE 1 Hospitalizations associated with cannabis use and a primary diagnosis of psychotic disorder or schizophrenia

Year	Hospitalization episodes due to PD with associated CU (*n*)	% from all schizophrenia and other psychotic disorders hospitalizations	Hospitalizations per 100,000 inhabitants	Mean age + *SD* (years)	Male sex (%/*n*)	Mean/median LoS (days)
2000	20	0.87	0.19	24.40 + 5.64	90.0/18	19.45/9.50
2001	24	0.91	0.23	27.79 + 7.72	91.7/22	21.83/20.00
2002	41	1.53	0.39	27.29 + 5.87	97.6/40	21.71/20.00
2003	61	1.75	0.58	26.90 + 7.23	82.0/50	21.97/19.00
2004	75	2.08	0.71	28.56+ 11.15	88.0/66	29.19/21.00
2005	99	2.72	0.94	27.57 + 7.41	91.9/91	30.21/20.00
2006	82	2.23	0.78	26.99 + 8.79	90.2/74	23.67/19.50
2007	93	2.43	0.88	27.67 + 8.24	94.6/88	20.66/16.00
2008	190	3.69	1.80	30.24 + 8.06	90.5/172	15.87/11.00
2009	185	3.51	1.75	29.65 + 8.20	92.4/171	15.77/12.00
2010	211	4.11	2.00	30.86 + 9.17	89.6/189	17.03/12.00
2011	259	4.98	2.46	30.58 + 9.63	91.1/236	18.08/16.00
2012	320	5.87	3.05	31.49 + 9.64	88.1/282	19.25/14.50
2013	453	8.28	4.34	31.55 + 9.48	88.7/402	19.06/14.00
2014	532	9.60	5.13	31.59 + 9.44	89.8/478	18.08/15.00
2015	588	10.60	5.69	31.84 + 9.63	88.9/523	20.37/16.00
Total	3,233	4.71	N.A.	30.66 + 9.30	89.8/2,902	19.42/15.00

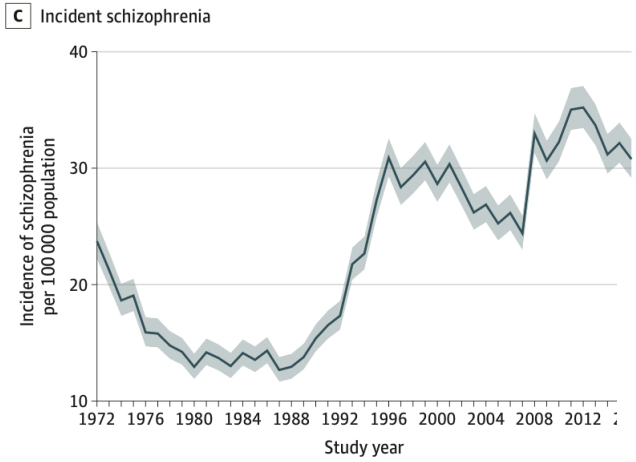
Abbreviations: CU, cannabis use; LoS, length of stay; PD, psychotic disorders.

Int J Methods Psychiatr Res. 2020

JAMA Psychiatry | Original Investigation

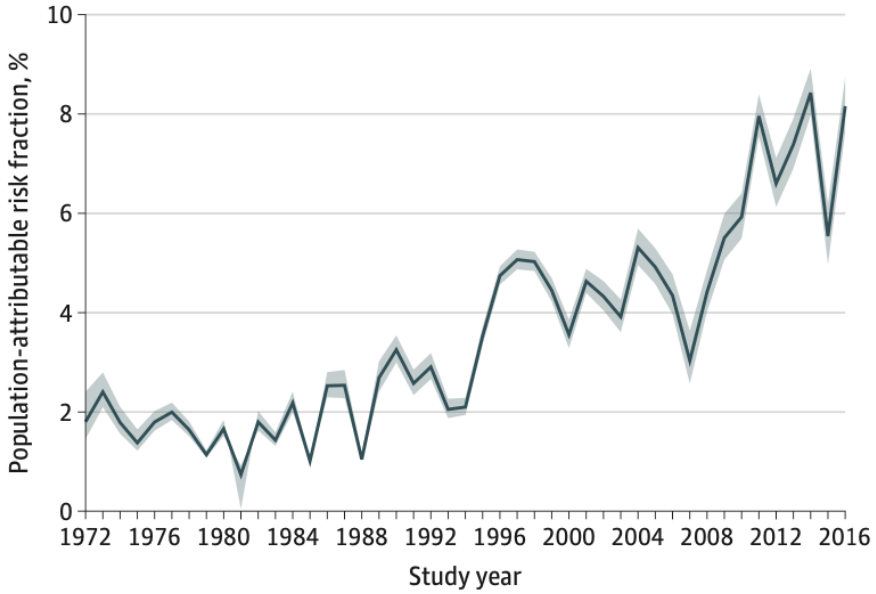
Development Over Time of the Population-Attributable Risk Fraction for Cannabis Use Disorder in Schizophrenia in Denmark

Carsten Hjorthøj, PhD; Christine Merrild Posselt, MSc; Merete Nordentoft, DrMedSc



During this period in Denmark both the consumption of cannabis and its potency have increased

Figure 2. Development of the Population-Attributable Risk Fraction (PARF) of Cannabis Use Disorder in Schizophrenia in Denmark



These PAFR are adjusted for several confounders

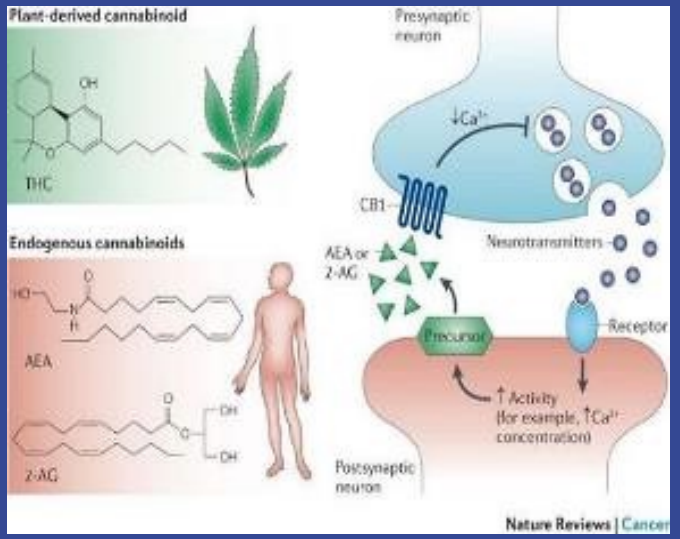
How does cannabis have any effect on our physiology?

A report from the International Cannabinoid Research Society (ICRS) published in *Nature* 2015 reminds us about …A PERSONABLE SYSTEM

Endocannabinoids (1st described 10 years ago) are everywhere

The Endocannabinoid system on demand (CB1-CB2 Receptors and more) is the pathway by which tetrahydrocannabinol (THC) exerts its effects on:

- Appetite, memory, alertness, pain, inflammation and bone health, and stimulation of the endocannabinoid system is associated with the protection of healthy cells
- "The endocannabinoid system helps us eat, sleep, relax, forget and protect our neurons"
- Endocannabinoid receptors are spread throughout the body…this could explain why the compounds found in cannabis seem to have no end of potential medical uses



Owens B. *Nature* 2015;**525**:S6–8.

The Endocannabinoid system: our CNS safety helmet and more

Regulates
Glutamate and
GABA transmission

Medicinal Cannabis has is now legal in UK from the1st of November 2019

But very few physician are prescribing it

Aspirin (acetylsalicylic acid)

Indications:

- Fever
- Inflammation
- Pain
- Rheumatic fever
- Blood clots
- Ischaemic Stroke

Adverse effect:

- Gastric bleeding
- Intra-cerebral haemorrhage
- Skin Swelling
- Reye's Disease *(do not give to children or adolescents to control fever!!!)*

Dose: 300 or 325 mgs tbs
75 or 81 mgs tbs
Interaction: e.g. NSAID

BNF, 2018.

Medicinal cannabis

(THC,CBD and plus hundred more cannabinoids):

Adverse effect:

- Transient Psychosis
- Psychotic Disorders (high THC)…*daily use; adolescent use…*
- Impaired Cognition (high THC)
- Reduced driving ability

Indications:

- Pain (Dronabinol synthetic THC)
- Intractable Nausea (Nabilone synthetic THC)
- Spasticity (Sativex THC-CBD…)
- Epilepsy (CBD)
- Inflammation (THC & ?)
- Schizophrenia/Psychosis (CBD)

Medicinal Cannabis Dose: ???????
Exact active Ingredients proportion ?????
Interactions ?????

Whiting PF, *et al. JAMA* 2015;**313**:2456–73.

What to consider before prescribing

Firstly:

1. Have clear evidence of efficacy for the condition
2. Are we looking at Cannabis extract with pure THC, CBD, both? Or samples from the whole plant?

Then:

- Family history of psychosis
- Previous History of Psychosis
- Keep the THC % as low as possible consider preparations including CBD as well (e.g. Sativex)
- Monitor for Psychotic symptoms especially paranoia (VR)
- Monitor for tolerance and Dependence/withdrawal when reducing /stopping
- Advice about driving

What about outcome in those who continue using drugs after psychosis onset?

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis

Tabea Schoeler, Anna Monk, Musa B Sami, Ewa Klamerus, Enrico Foglia, Ruth Brown, Giulia Camuri, A Carlo Altamura, Robin Murray, Sagnik Bhattacharyya

Summary

Background Although the link between cannabis use and development of psychosis is well established, less is known about the effect of continued versus discontinued cannabis use after the onset of psychosis. We aimed to summarise available evidence focusing on the relationship between continued and discontinued cannabis use after onset of psychosis and its relapse.

Lancet Psychi
Published Onl
January 14, 2016
http://dx.doi.org/10.1016/
52215-0366(15)00363-6

Interpretation Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in pa

Effects of continuation, frequency, and type of cannabis u on relapse in the first 2 years after onset of psychosis: an observational study

Tabea Schoeler, Natalia Petros, Marta Di Forti, Ewa Klamerus, Enrico Foglia, Olesya Ajnakina, Charlotte Gayer-Anderson, Marco Colizzi, Diego Quattrone, Irena Behlke, Sachin Shetty, Philip McGuire, Anthony S David, Robin Murray, Sagnik Bhattacharyya

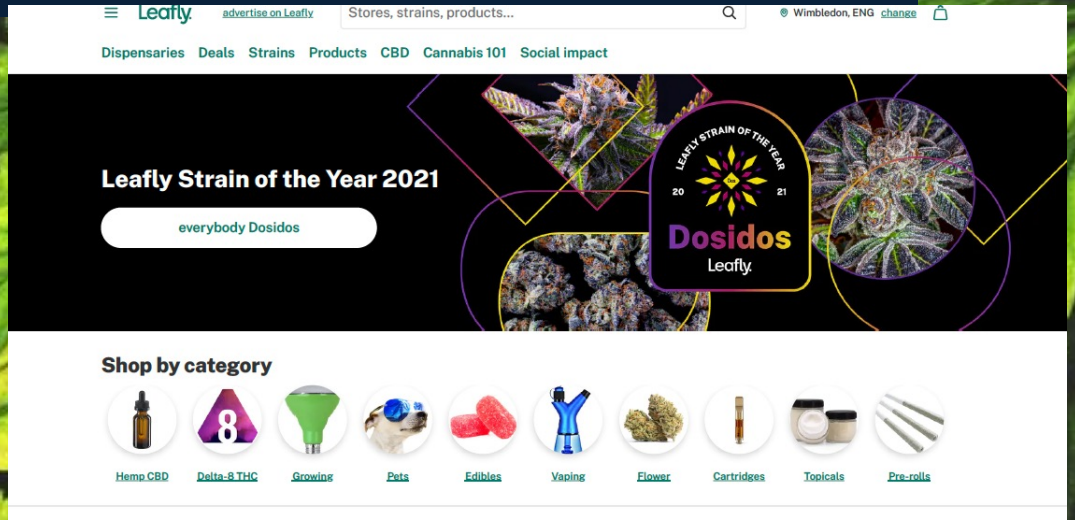
Findings Between April 12, 2002, and July 26, 2013, 256 patie
follow-up assessments for these patients until September, 2
of cannabis who stopped after the onset of psychosis had the
In multiple analysis, continued high-frequency users (ie, da
cannabis had the worst outcome, indexed as an increased ri
CI 1·22–9·18), more relapses (incidence rate ratio 1·77; 95%
(*b* –0·22; 95% CI –0·40 to –0·04), and more intense psychiat
psychosis.

Schoeler T, *et al. Lancet Psychiatry* 2016;**3**:215–25.

Present and Future:

Cannabis already in Space and soon legal in London

From the street to the web with great claims of pleasure+safety+benefits



In 2022 what do you find on the web

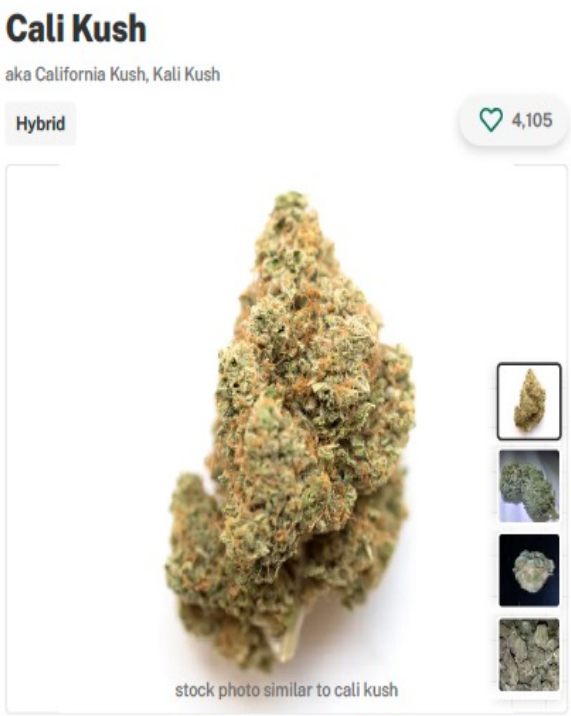
Great weed you can find today.

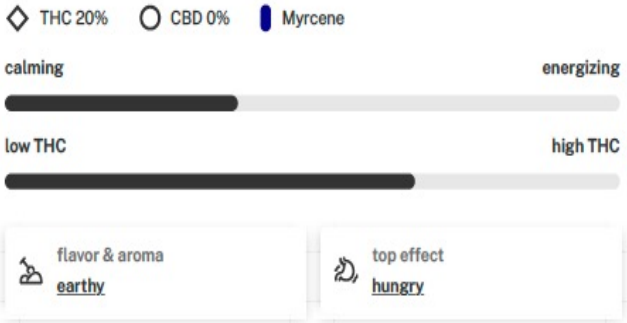
These are all found near Wimbledon, ENG

Top happy strain in your area	Top euphoric strain in your area	Top aroused strain in your area
		
MAC	**Gelato**	**Cheetah Piss**
aka Miracle Alien Cookies, Miracle Cookies	aka Gelato 42, Larry Bird	
4.6 ★★★★★ (382)	4.6 ★★★★★ (2028)	4.6 ★★★★★ (95)
Hybrid ◇ THC 22% ▽ CBG 1%	Hybrid ◇ THC 16% ○ CBD 0%	Hybrid ◇ THC 19% ▽ CBG 1%
learn more	ore	more

"*Dreaming California*" : Cali in London

"You can bulk buy all of your plastic bags and stickers online for £50, max," reveals Dave, a dealer based in the North East. "By putting your buds inside one of the bags, your overall profits will grow by at least 30%"

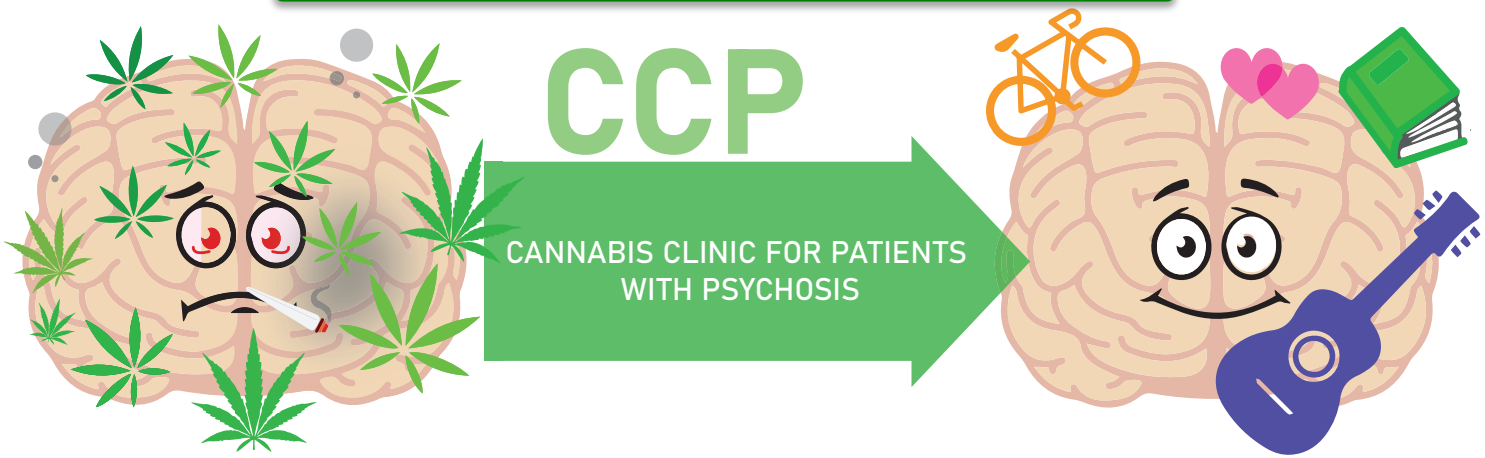




“The way to get started is to quit talking and begin doing.”
All our dreams can come true, if we have the courage to pursue them."

Our newly developed Service

The CCP is the first clinical service in the country offering to young adults suffering their first episode of psychosis the opportunity to significantly reduce and/or stop their cannabis use



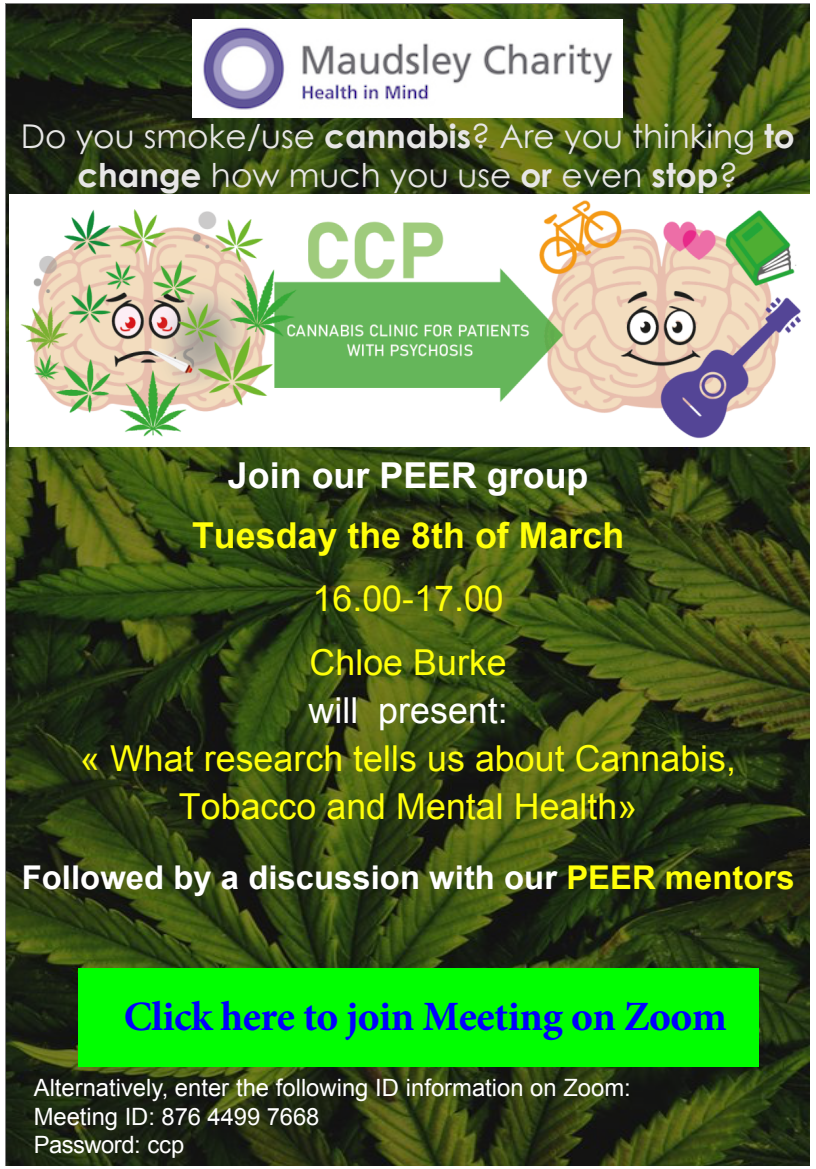
- Initial funds from the Maudsley Charity one to one intervention and PEER group
- Maudsley Charity funds to expand the PEER group and create an e-learning package

Maudsley Charity
Health in Mind

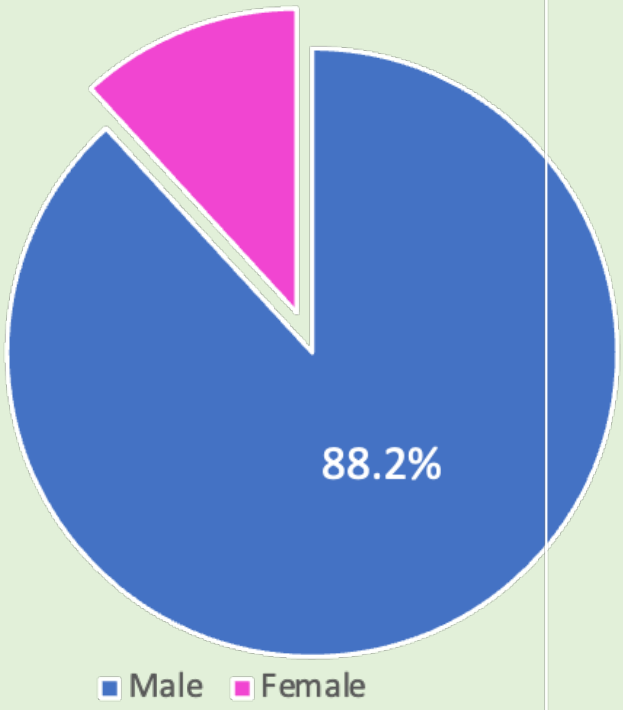
Our recipe if you cannot get local resources and you have little support:

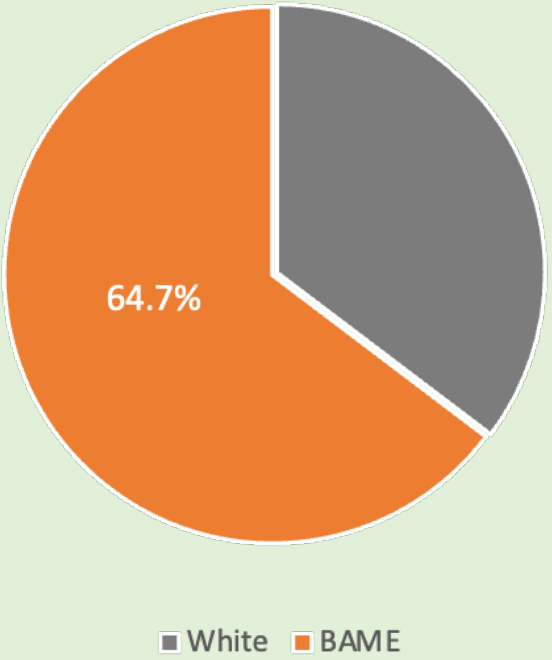
1. Bring togethers all your local experts (start with friends)
2. Summarise the evidence that support your idea
3. *Engage the nursing staff and your clinical colleagues, patients and carers and ask them what they need*
4. Look for some funding
5. Involve students and trainees
6. Begin with a simple model
7. Measure its impact

Born in the Pandemic, cheap to run and able to reach many

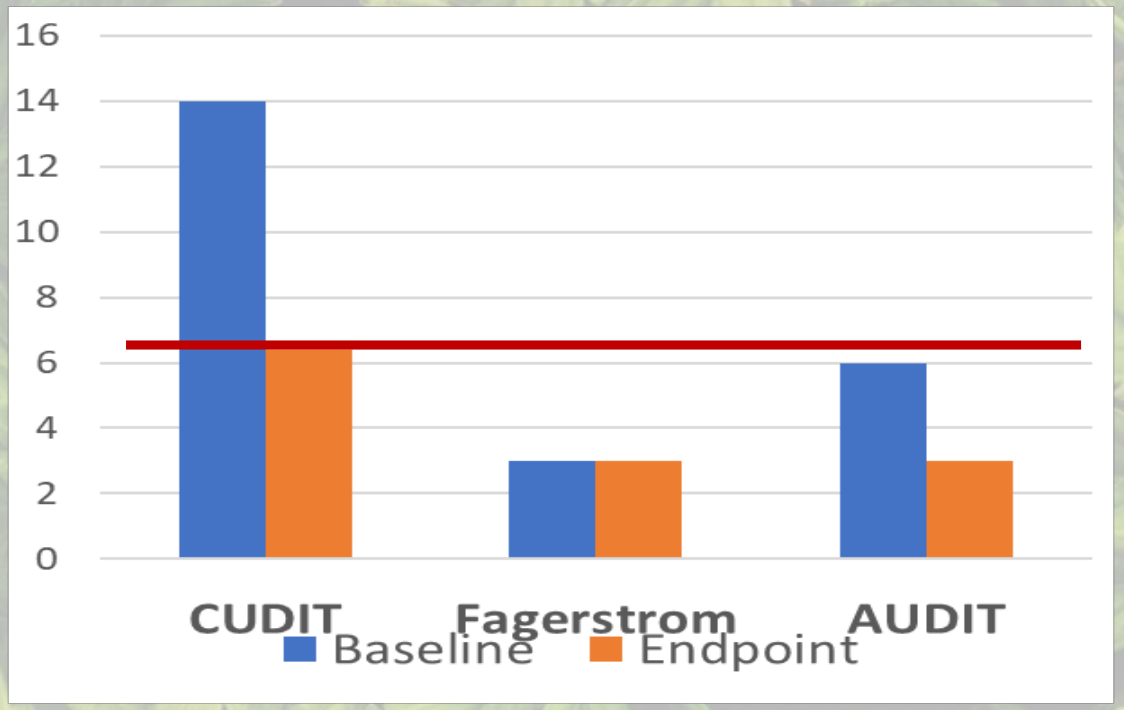


Gender and Ethnic Background of the first 17 YA referred to the CCP who completed the intervention





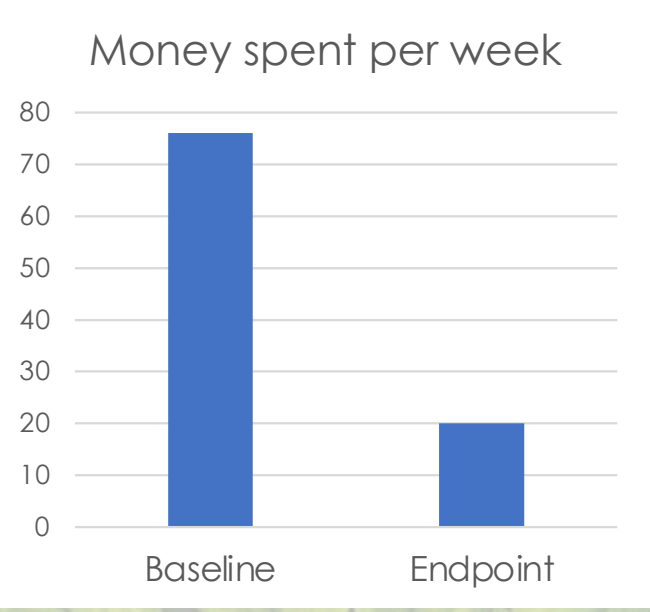
Outcomes comparison between baseline (at time of referral to the CCP) and endpoint (after completing the intervention) for the first 17 YA that received the CCP intervention



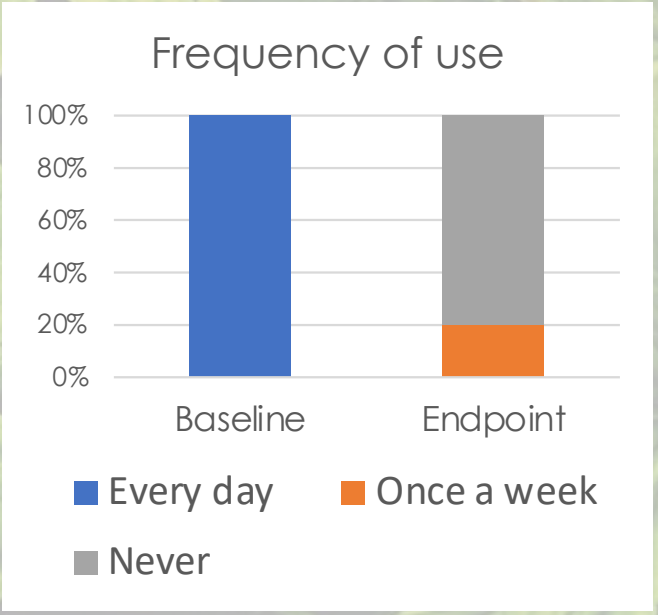
*The red line represents the CUDIT score threshold for Cannabis Dependence

This bar chart illustrates baseline and follow up comparison in the measures cannabis dependence (CUDIT), tobacco dependence (Faferstom) and alcohol dependence (AUDIT)

Outcomes comparison between baseline (at time of referral to the CCP) and endpoint (after completing the intervention)

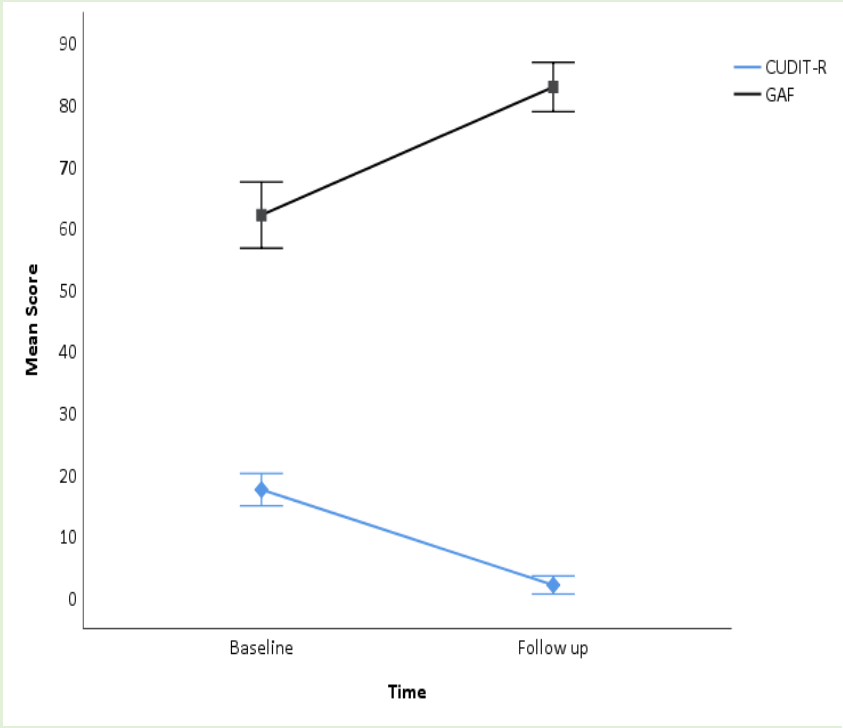


The above graph reports money spent on average x week at baseline and follow up by the 17 YA who completed their CCP intervention



The above graph reports the frequency of cannabis use at baseline and follow upby the 17 YA who completed their CCP intervention

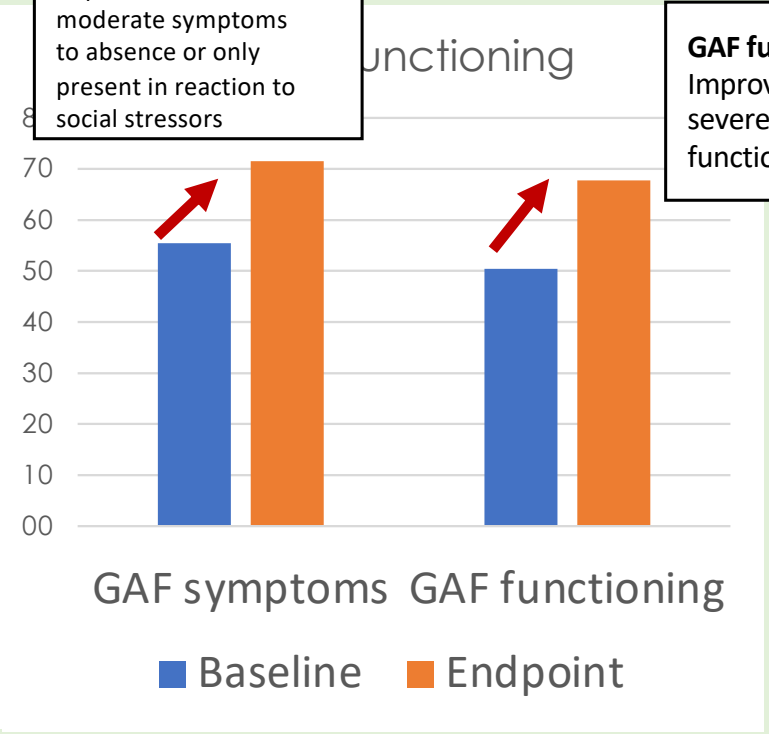
Changes in Cannabis use and Level of functioning



The above graph illustrates that with the reduction in cannabis use (**mean CUDIT-Score**) between starting the CCP intervention (baseline) and completing it (follow up) the level of function (**mean GAF-scores**) increases

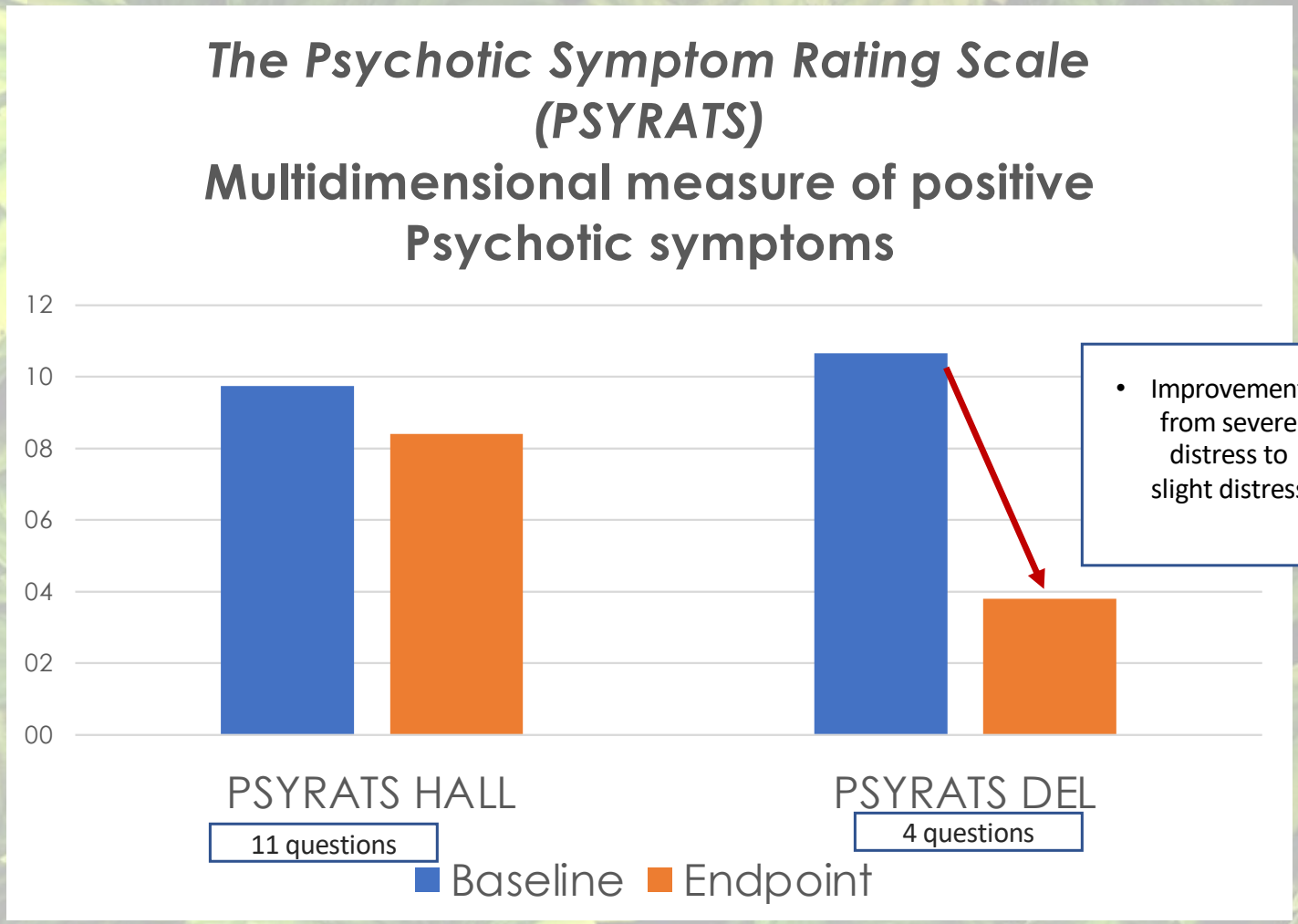
GAF symptoms: Improvement seen from moderate symptoms to absence or only present in reaction to social stressors

GAF functioning: Improvement from severe impairment of functioning to mild

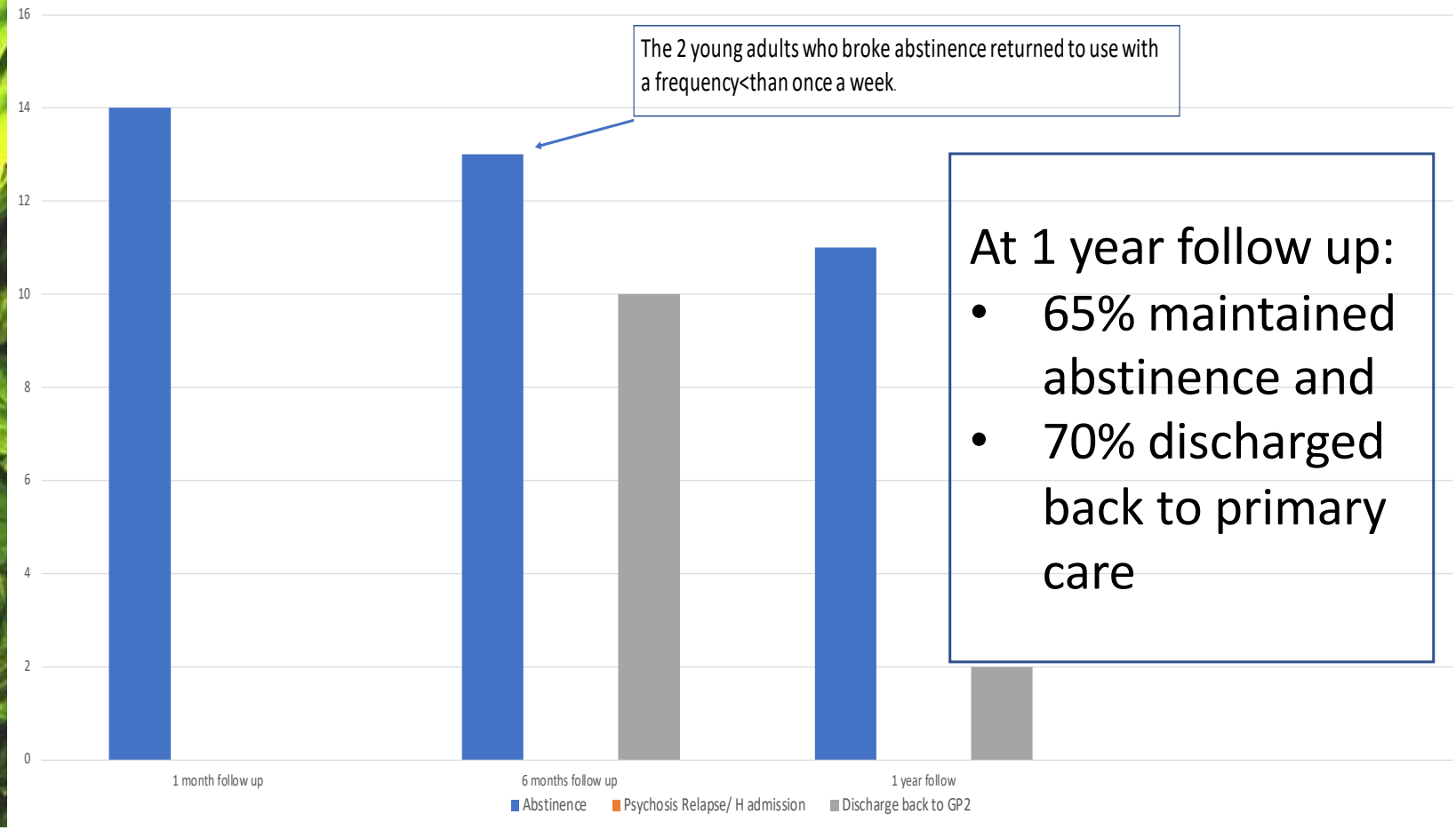


The above chart shows the changes between baseline (start of CCP intervention) and at end of treatment (end-point) in both : GAF symptoms and GAF functioning mean score)

Outcome comparison between baseline and endpoint



CCP Preliminary follow up on the 14/17 patients that achieved cannabis abstinence



At 1 year follow up:

- 65% maintained abstinence and
- 70% discharged back to primary care

HOW SKUNK BLEW OUR MINDS

Cannabis is far stronger than it used to be and psychosis levels are soaring. *Megan Agnew* meets recovering smokers — and the medics helping to restore their sanity

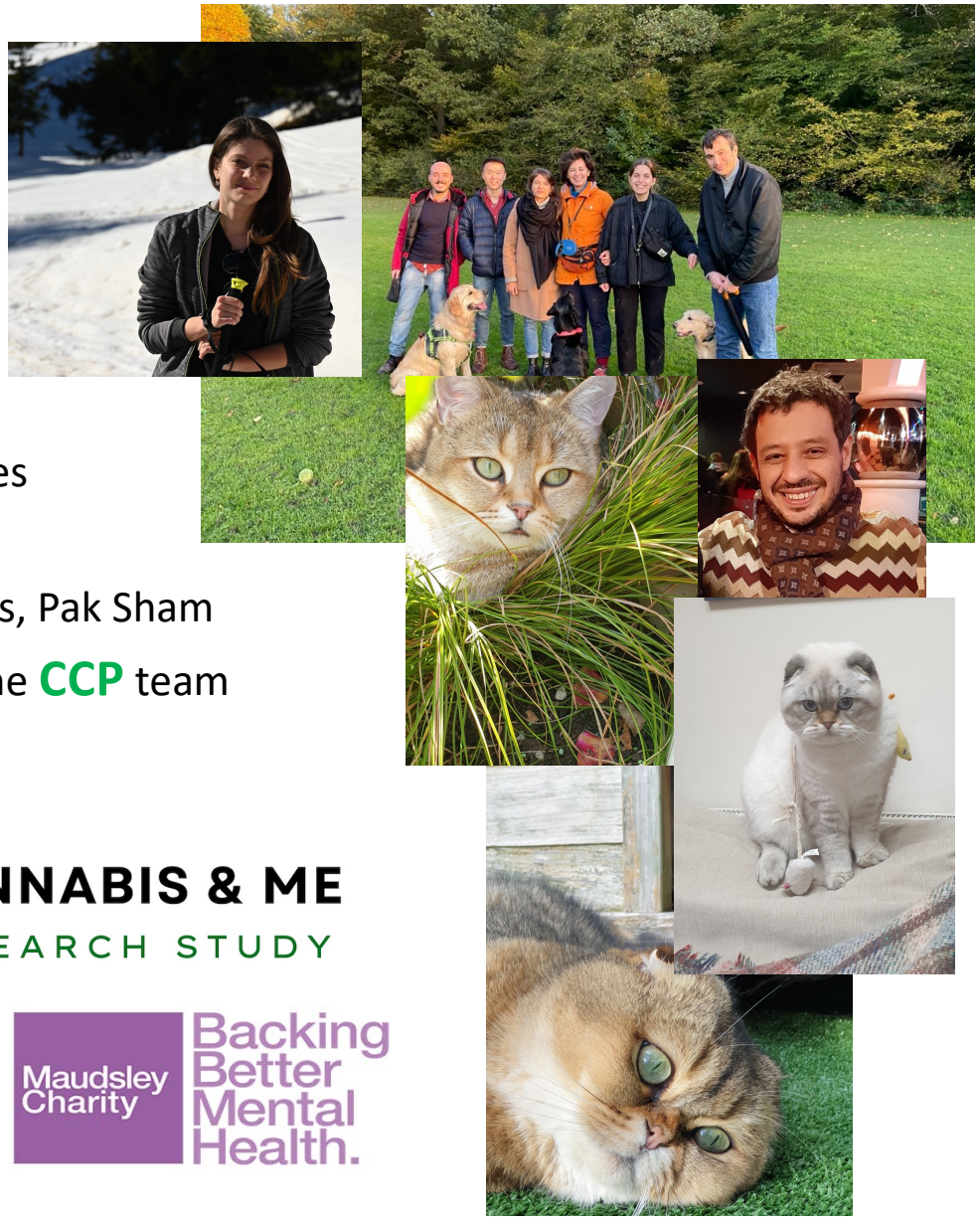
"NOW, WITH THE CLINIC, I'M LOOKING AT LIFE IN A WHOLE DIFFERENT WAY. MY BRAIN IS STARTING TO WORK AGAIN, I'M DOING AN APPRENTICESHIP. IT HAS CHANGED MY LIFE"

mental health."

Ad Gridley, the former smoker who recovered from his psychosis, certainly wishes he'd been made more aware of the consequences. "I wish I'd known there were proper downsides to it," he says. "I thought my mind would never turn on me. A couple of years later I found that I couldn't hear myself think. The cannabis clinic sessions… I've forgotten what I was going to say — memory loss. It does happen," he trails off. "There is a negative imprint left on my brain. All these years later and I can still feel it." ■

Some names have been changed

Last but not least



My gratitude to:

- To the wonderful **first episode psychosis patients** who I see in my Clinic and who have participated in our studies
- All the **EUGEI teams**
- Robin Murray, Emma Johnson, Evangelos Vassos, Pak Sham
- And my **Cannabis&Me** research team and the **CCP** team & my/our wonderful pets

CCP
CANNABIS CLINIC FOR PATIENTS WITH PSYCHOSIS

CANNABIS & ME
RESEARCH STUDY

UKRI Medical Research Council

Maudsley Charity Backing Better Mental Health.