Changes in cannabis potency and first-time admissions to drug treatment: A sixteen-year study in the Netherlands

Tom P Freeman[1,2*], Peggy van der Pol[3], Wil Kuijpers[4], Jeroen Wisselink[4], Ravi K Das[2], Sander Rigter[3], Margriet van Laar[3], Paul Griffiths[5], Wendy Swift[6], Raymond Niesink[3], Michael T Lynskey[1]

1. National Addiction Centre, King's College London, United Kingdom
2. Clinical Psychopharmacology Unit, University College London, United Kingdom
3. Trimbos Institute, Netherlands Institute of Mental Health and Addiction, Utrecht, the Netherlands
4. Stichting Informatievoorziening Zorg, National Alcohol and Drugs Information System, Houten, the Netherlands
5. European Monitoring Centre for Drugs and Drug Addiction, Portugal
6. National Drug and Alcohol Research Centre, UNSW Australia, Sydney, NSW, Australia

*Address correspondence to:
Tom Freeman
National Addiction Centre
King's College London
tom.freman@kcl.ac.uk

Abstract: 244/250

Main text: 3,980/4500

Key words: Cannabis; delta-9-tetrahydrocannabinol; potency; addiction, mental health, psychosis, drug treatment

Abstract

Background: The number of people entering specialist drug treatment for cannabis problems has increased considerably in recent years. The reasons for this are unclear, but rising cannabis potency could be a contributing factor.

Methods: Cannabis potency data were obtained from an ongoing monitoring programme in the Netherlands. We analysed concentrations of delta-9-tetrahydrocannabinol (THC) from the most popular variety of domestic herbal cannabis sold in each retail outlet (2000-2015). Mixed effects linear regression models examined time-dependent associations between THC and first-time cannabis admissions to specialist drug treatment. Candidate time lags were 0-10 years, based on normative European drug treatment data.

Results: THC increased from a mean (95% CI) of 8.62 (7.97, 9.27) to 20.38 (19.09, 21.67) from 2000-2004 and then decreased to 15.31 (14.24, 16.38) in 2015. First-time cannabis admissions (per 100,000 inhabitants) rose from 7.08 to 26.36 from 2000-2010, and then decreased to 19.82 in 2015. THC was positively associated with treatment entry at lags of 0-9 years, with the strongest association at 5 years, b=0.370 (0.317, 0.424), $p<0.0001$. After adjusting for age, sex and non-cannabis drug treatment admissions, these positive associations were attenuated but remained statistically significant at lags of 5-7 years and were again strongest at 5 years, b=0.082 (0.052, 0.111), $p<0.0001$.

Conclusions: In this sixteen-year observational study, we found positive time-dependent associations between changes in cannabis potency and first-time cannabis admissions to drug treatment. These associations are biologically plausible, but their strength after adjustment suggests that other factors are also important.

Introduction

Cannabis is used by an estimated 183 million people, and accounts for around half of all first-time admissions to specialist drug treatment worldwide (UNODC, 2016). The number of people entering specialist drug treatment for cannabis problems has risen considerably in recent years. Across Europe, there was a 53% increase in first-time clients between 2006 and 2014, and cannabis has now superseded opiates as the primary problem drug (EMCDDA, 2016). These changes highlight a concerning increase in population markers of burden and morbidity attributable to cannabis. There are no approved pharmacotherapies for the treatment of cannabis use disorders, and psychosocial interventions have limited efficacy (Curran *et al.*, 2016). The increase in cannabis admissions, alongside a lack of evidence-based interventions creates a significant challenge for treatment providers (Monaghan *et al.*, 2016). Clients entering specialist drug treatment with cannabis as a primary problem have shown the poorest treatment outcomes at six months (rates of abstinence and reduction in use) of all illicit drugs (NDTMS, 2014).

Interestingly, cannabis-related treatment admissions have continued to rise in some regions despite stable or decreasing prevalence of use estimates, including Germany, Spain and the UK (UNODC, 2016). There are several possible reasons for this, including changes in treatment availability, attitudes towards cannabis, or that cannabis is becoming an increasingly harmful substance. The primary psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC), which has dose-related effects on drug reinforcement, memory impairment and psychotic-like symptoms (Curran *et al.*, 2016). Concentrations of THC have risen considerably in the US (ElSohly *et al.*, 2016), UK (Potter *et al.*, 2008) and worldwide (Cascini *et al.*, 2012) in recent decades. For example, a study of illicit cannabis samples in the US (ElSohly *et al.*, 2016) suggested that THC concentrations rose from a mean of 4% in 1995 to 12% in 2014. More recently, a dramatic rise in potency was reported within two years of legal sales in Washington State, where extremely high-potency extracts (~70% THC) now comprise around 20% of purchases (Smart *et al.*, 2017).

Use of cannabis products with high concentrations of THC has been linked to poorer mental and addiction health outcomes (Chan *et al.*, 2017, Di Forti *et al.*, 2015, Freeman and Winstock, 2015, Meier, 2017, Schoeler *et al.*, 2016). A cross-sectional online survey (Freeman and Winstock, 2015) found that use of cannabis with high THC content was more strongly associated with cannabis dependence than lower potency forms of cannabis. Moreover, this association was found to be stronger in younger cannabis users. A second cross-sectional online survey found that use of extremely-high potency cannabis concentrates (Butane Hash Oil) was associated with greater physical dependence on cannabis, and this association was robust after accounting for possible confounds using both covariate adjustment and propensity score matching (Meier, 2017). Prospective studies have reported an association between degree of cannabis exposure and transition to cannabis dependence (Silins *et al.,* 2014), although not in those who are using cannabis (near) daily at baseline (van der Pol *et al.*, 2013a). Naturalistic studies suggest that cannabis users only partially adapt their smoking behaviour to differences in cannabis potency (Freeman *et al.*, 2014, van der Pol *et al.*, 2014). Taken together, it is plausible that long-term changes in cannabis potency could influence cannabis-related harms (including changes in cannabis admissions to drug treatment). Although the potential health impacts of increasing cannabis potency have been widely acknowledged (Di Forti *et al.*, 2015, ElSohly *et al.*, 2016, EMCDDA, 2016, Freeman and Winstock, 2015, McLaren *et al.*, 2008, UNODC, 2016) we are unaware of any previous attempts to empirically test associations between changes in cannabis potency and population markers of cannabis harms.

Effective monitoring of cannabis potency can play a critical role in estimating the potential health impact of cannabis use in different regions. However, high-quality and long-term monitoring programmes are extremely rare (Freeman and Swift, 2016). Of those available, the Trimbos Institute potency monitor (Niesink *et al.*, 2015, Pijlman *et al.*, 2005) offers the highest quality evidence and is the most suitable resource for testing associations between changes in potency and cannabis harms. Firstly, cannabis samples are purchased directly at the retail level from 'coffee shops' using randomised sampling. This method is advantageous to other studies utilising cannabis samples from police seizures, which may be biased by law enforcement methods (Nguyen and Reuter, 2012), sampling bias, and variation in sample degradation during storage (Sevigny, 2013). Secondly, in contrast to linear increases in cannabis potency reported elsewhere (ElSohly *et al.*, 2016), THC concentrations have both risen (Pijlman *et al.*, 2005) and then subsequently declined (Niesink *et al.*, 2015) in the Netherlands during the last sixteen years, providing a unique opportunity to detect similar changes in cannabis-related problems (Freeman and Swift, 2016). Here we sought to test whether changes in cannabis potency (THC) are associated with rates of first-time cannabis admissions to specialist drug treatment in the Netherlands from 2000-2015. This study was reported according to the STROBE (strengthening the reporting of observational studies in epidemiology) statement.

Methods

We combined two national sixteen-year datasets to examine whether there are time-dependent associations between annual estimates of cannabis potency, and the number of first-time cannabis admissions to drug treatment.

Cannabis potency

In the Netherlands, cultivation of cannabis plants is a criminal offence. However the government officially condones the sale of cannabis from 'coffee shops' under strict conditions (Monshouwer *et al.*, 2011). Coffee shops are estimated to account for >70% of cannabis sales in the Netherlands (Wouters and Korf, 2009). Since 2000, the Trimbos Institute has conducted anonymous test purchases from a random selection of these coffee shops (50 outlets each year plus reserves) to monitor changes in potency (Niesink *et al.*, 2015, Pijlman *et al.*, 2005). Purchases were conducted in January each year to control for seasonal variation, and immediately sent for analysis (maximum storage time three weeks at ambient temperature). Delta-9-Tetrahydrocannabidiol (THC), cannabidiol (CBD) and cannabinol (CBN) concentrations were extracted using capillary gas chromatography with flame ionisation detection. All analysis took place at DeltaLab (the Netherlands) using standardized, internally audited and externally cross-validated methods. Further details are provided elsewhere (Niesink *et al.*, 2015, Pijlman *et al.*, 2005).

Four different cannabis products were purchased from each retail outlet as part of the standardised protocol. Therefore, the number of samples collected for each type did not necessarily reflect their overall prevalence at retail outlets. For this reason, we did not combine data across all cannabis types, as the number of samples for each type could have biased our estimates of national cannabis potency. However, randomised sampling across successive years provided a reliable measure of change within individual cannabis products. Therefore, in order to provide the most reliable and valid estimates of national cannabis potency, we used data from a single product, purchases of the most popular variety of domestically grown herbal cannabis ('Nederwiet') sold at each coffee shop. This variety of cannabis was chosen as it is by far the most commonly consumed cannabis product in the Netherlands (Niesink *et al.*, 2015, Schubart *et al.*, 2011, van der Pol *et al.*, 2013b, Van Laar *et* *al.*, 2016). Nederwiet is a Dutch term for high-potency, indoor grown herbal cannabis. It is sometimes referred to as 'sinsemilla' or 'skunk' and is also the most common type of cannabis in the UK (Freeman *et al.*, 2014, Potter *et al.*, 2008) USA (ElSohly *et al.*, 2016) and Australia (Swift *et al.*, 2013).

First-time admissions to drug treatment

First-time admissions to specialist drug treatment can be used as a proxy for problematic drug use within a given region (UNODC, 2016) and offer a valid indicator of changes in burden and morbidity attributable to a particular substance. Since 1994, all Dutch drug treatment data (inpatient, outpatient, rehabilitation) have been compiled into the National Alcohol and Drugs Information System (LADIS) database, on behalf of the Ministry of Health, Welfare and Sports (Wisselink *et al.*, 2016). Institutions for addiction care and addiction care rehabilitation provide complete data to Stichting Informatievoorziening Zorg (IVZ) on an annual basis, and the database is internally audited. Each client is identified through a unique pseudonym identification code to prevent duplicate cases. For the purposes of this study, annual data (2000-2015) were compiled for the following:

(1) The number of first-time admissions with cannabis as the primary drug.

(2) Mean age and sex of first-time admissions with cannabis as the primary drug.

(3) The number of first-time non-cannabis admissions: primary problems with other drugs (alcohol, opiates, cocaine, amphetamine, and ecstasy), after excluding any clients with a secondary cannabis problem.

Data for (1) and (3) were normalised to the annual national population (Central Statistical Office, the Netherlands) and expressed as the number of people per 100,000 inhabitants (total population), in line with previous analysis of Dutch drug treatment data (Brunt *et al.*, 2010).

Statistical analysis

Statistical analyses were conducted using STATA/SE 14. Among European clients entering specialist drug treatment for cannabis, the mean age of first cannabis use is 16, and the mean age of first treatment entry is 26 (EMCDDA, 2016). Using this 10-year lag as a normative window of biological plausibility, we tested associations between THC and first-time cannabis admissions at candidate time lags of 0-10 years. Due to evidence of autocorrelation in linear regression models, we conducted linear mixed effects models with THC as a fixed effect, and calendar year (Year) as a random effect, with first-time cannabis admissions as the outcome variable. Each of the individual cannabis samples were entered as separate data points for THC concentration, and Year (2000-2015) was coded as 0-15. Separate models were tested at each candidate time lag using maximum likelihood estimation. A Bonferroni correction was applied to each of these 11 time-lagged models, resulting in an adjusted α threshold of 0.0045. As each candidate time lag had a different number of observations (fewer as the lag increased), comparisons between different time lags were was based upon the magnitude of the unstandardized regression coefficient (i.e. the strength of the association between THC and first-time treatment admissions) rather than the significance level. In order to investigate the impact of adjusting for relevant confounds, these were added as fixed effects to the aforementioned models. There were no missing data.

Results

Cannabis potency and drug treatment

THC concentrations were available for 969 unique cannabis samples from 2000-2015. The mean number of samples purchased each year was 60.56 (range: 53-66). THC increased from 2000-2015. As shown in Figure 1, this reflected an initial increase from 8.62 (7.97, 9.27) to 20.38 (19.09, 21.67) from 2000-2004. Thereafter, THC decreased to 15.31 (14.24, 16.38) in 2015. The number of first-time cannabis admissions (per 100,000 inhabitants) also increased from 2000-2015. As shown in Figure 1, there was an initial increase of 7.08 to 26.36 from 2000-2010. This was followed by a decrease to 19.82 from 2010-2015 (Figure 1).

<FIGURE 1>

Time-dependent associations between cannabis potency and drug treatment

Positive associations were found between THC and first-time cannabis admissions at time lags ranging from 0 to 9 years, with the strongest relationship at a 5-year lag, as shown in Table 1 (Model 1, unadjusted), b=0.370 (0.317, 0.424), $p<0.0001$. These findings are consistent with the possibility that cannabis potency may have contributed to first-time cannabis admissions in a time-dependent manner. Based on these estimates, each 1% increase in THC was associated with a 0.370 (0.317, 0.424) rise in first-time admissions per 100,000 inhabitants. This equates to an estimated 60.765 (52.061, 69.633) people in the Netherlands based on the mean population between 2000 and 2015.

<TABLE 1>

Testing alternative explanations

First-time cannabis admissions were negatively associated with clients' age at treatment entry (Supplementary Figure 1) and negatively associated with male sex (Supplementary Figure 2). Adjusting for age and sex attenuated the positive associations between THC and first-time treatment entry. However they remained significant at time lags of 0 years and 4-7 years, Table 1 (Model 2, adjusted for age and sex). The strongest relationship was found at a 5-year lag.

Previous research suggests that CBD may offset some of the harmful effects of THC (Colizzi and Bhattacharyya, 2017, Englund *et al.*, 2017). Moreover, levels of CBN in cannabis can provide an indicator of THC degradation following extended sample storage (Sevigny, 2013). However, as is typical for this type of cannabis (Nederwiet; domestically grown herbal cannabis), mean (95% CI) concentrations were high for THC, 15.55 (15.26, 15.85) but extremely low or absent for CBD, 0.30 (0.27, 0.34) and CBN, 0.14 (0.13, 0.16). CBD and CBN concentrations were therefore not included as covariates (Supplementary Figure 3).

Prevalence of cannabis use provides an alternative explanation for changes in first-time cannabis admissions. We extracted data from the Dutch school survey (age 12-16), which were available from 1999, 2003, 2007, 2011 and 2015. Prevalence estimates for last month cannabis use decreased from 8.5% in 1999 through to 4.9% in 2015, and a linear model showed very strong fit to the data (R^2 = 0.97). Data were also available for adults (age 15-64) from 2001, 2005, 2009, 2014 and 2015. Estimated prevalence of last month use increased from 3.4% to 5.3% in 2015. A linear model again showed very strong fit to the data (R^2 = 0.85). On the basis of the prevalence data available, these linear trends are unlikely to explain the non-linear changes in first-time cannabis admissions, and therefore were not included as covariates (Supplementary Figure 4).

Next, in order to account for changes common to drug treatment in general, we extracted data for all non-cannabis admissions (first-time admissions of alcohol, opiates, cocaine, amphetamines, ecstasy), after excluding any clients with cannabis as a secondary problem (Supplementary Figure 5). Adjusting for non-cannabis admissions (in addition to age and sex) further attenuated positive associations between THC and cannabis admissions. Significant associations remained at lags of 5-7 years, as show in Table 1 (Model 3, adjusted for age, sex and non-cannabis admissions). The strongest relationship was found at a 5-year lag, b=0.082 (0.052, 0.111), $p<0.0001$. Based on these estimates, each 1% increase in THC was associated with a 0.082 (0.052, 0.111) rise in first-time admissions per 100,000 inhabitants. This equates to an estimated 13.467 (8.540, 18.229) people in the Netherlands based on the mean population between 2000 and 2015. The level of attenuation was similar when we adjusted for specific drugs showing the most similar profile to cannabis on the basis of raw data (Supplementary Figure 6) and change from baseline (Supplementary Figure 7). As shown in Supplementary Table 1, positive associations between THC and cannabis admissions remained significant at lags of 5-7 years after adjusting for age, sex and alcohol admissions (Model 3b) as well as age, sex and amphetamine admissions (Model 3c). In both of these models, the strongest association was again found at a 5-year lag.

Discussion

Cannabis potency continues to rise in a number of states and countries (Cascini *et al.*, 2012, ElSohly *et al.*, 2016, Potter *et al.*, 2008, Smart *et al.*, 2017). Meanwhile, cannabis problems now account for a substantial and increasing number of admissions to specialist drug treatment worldwide (EMCDDA, 2016, UNODC, 2016). National estimates of domestic herbal cannabis potency (THC) and first-time cannabis admissions to drug treatment showed matching profiles of change (sharp rise followed by gradual decline) in the Netherlands from 2000-2015. Using mixed effects linear regression models, we found time-dependent associations between THC and first-time treatment entry at lags of 0-9 years, with the strongest association at 5 years. These time lags are biologically plausible because they occur within the normative duration (10 years) between first trying cannabis and first-time entry to European drug treatment (EMCDDA, 2016) in which effects of cannabis potency are most likely to occur. These associations were attenuated after adjusting for client demographics and non-cannabis admissions, although positive associations remained statistically significant at lags of 5-7 years and were again strongest at 5 years. To our knowledge, this is the first study to investigate associations between changes in cannabis potency and health-related outcomes.

Since 2000, cannabis has become the primary illicit drug responsible for first-time admissions to specialist drug treatment, superseding opiates and cocaine. These trends have been evident in several countries including the Netherlands, but also across Europe as a whole (EMCDDA, 2016). A recent analysis of data submitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (Montanari *et al.*, 2017) found evidence for increasing cannabis admissions across 16 of the 22 countries examined. The authors speculated that these changes could be due to several factors, including an increase in cannabis use, cannabis potency, and changes in drug treatment services (Montanari *et al.*, 2017). Our findings provide novel insight into these potential explanations.

Changes in cannabis potency (but not prevalence of use, based on the available data), offers a potential explanation for these trends in the Netherlands between 2000 and 2015. Our findings add to existing evidence for a relationship between cannabis potency and poorer mental health and addiction outcomes (Chan *et al.*, 2017, Di Forti *et al.*, 2015, Freeman and Winstock, 2015, Meier, 2017, Schoeler *et al.*, 2016). They also highlight the extent to which potency can fluctuate over time within a single cannabis product (high-potency domestic herbal cannabis), which is the most common type available in the Netherlands (Niesink *et al.*, 2015, Schubart *et al.*, 2011, van der Pol *et al.*, 2013b, Van Laar *et al.*, 2016) UK (Freeman *et al.*, 2014, Potter *et al.*, 2008) USA (ElSohly *et al.*, 2016) and Australia (Swift *et al.*, 2013). This suggests that clinicians working with cannabis problems should not rely on classification of cannabis type alone to assess cannabinoid exposure and possible consequences of use. These data were collected in a single geographical region, and improved global monitoring of cannabis potency and health-related outcomes may be necessary to investigate these associations elsewhere (Freeman and Swift, 2016). However, our findings highlight a cause for concern regarding the health impact of extremely potent cannabis concentrates (~70% THC) which have very recently risen in popularity in some parts of the United States (Smart *et al.*, 2017). In a rapidly changing cannabis climate, it is essential that policy makers consider the effects of new legislation on cannabis potency and the incidence of cannabis-related harms.

If cannabis potency does contribute to drug treatment admissions (which cannot be established on the basis of this single observational study), our finding that the strongest association occurred at 5 years (extending to 7 years in fully adjusted models) suggests that this effect occurs at a mid-early stage in cannabis use trajectories. On the basis of these time lags, a typical client who started using cannabis at 16 and first entered treatment at 26 might be especially susceptible to variation in potency between the ages of 19-21. This could potentially reflect the timing of transition to cannabis use disorder in a typical user (Behrendt *et al.*, 2009). However, cannabis use trajectories are likely to vary substantially across individuals, and may oscillate between periods of daily or occasional use. Previous research indicates that the association between degree of cannabis use and cannabis use disorders is stronger in younger people (Courtney *et al.*, 2017). This may be in part due to *age-related* differences in sensitivity to THC (Mokrysz *et al.*, 2016). Moreover, *inexperienced* cannabis users may be especially vulnerable to changes in potency due to their lack of tolerance (D'Souza *et al.*, 2008) and inability to estimate the potency of their own cannabis (Freeman *et al.*, 2014). Long-term prospective cohort studies are needed to investigate these issues further. One previous study employing a comprehensive set of cannabis exposure variables, including potency, found no relationship between cannabis use variables and three-year incidence of DSM-IV-TR cannabis dependence (van der Pol *et al.*, 2013a). However, all participants were (near) daily users at baseline. It is therefore possible that variation in cannabis exposure is only associated with transition to dependence in younger and/or less experienced users, such as during adolescence (Silins *et al.*, 2014).

Although our data are consistent with the possibility that cannabis potency may have contributed to first-time cannabis admissions, the strength of association after adjustment suggests that other factors are also important. For example, there was a transient (one year) rise in treatment admissions for all drugs in 2007 (although cannabis admissions continued rising to 2010). Moreover, both cannabis and non-cannabis admissions decreased between 2013 and 2015. This could be attributable to the introduction of three-tier stepped care from January 2014, resulting in fewer people in addiction care being registered by the National Alcohol and Drugs Information System database (EMCDDA, 2014). Increases in cannabis admissions were also associated with a decline in the proportion of treatment seekers who were male, as well as a reduction in their age at treatment entry. These changes could be due to treatment-seeking or referral practices resulting in the admission of new clients independently of cannabis exposure, and/or other factors (such as rising cannabis potency) increasing problematic use in people who would not otherwise present to treatment services (i.e. younger and/or female clients).

This study had several strengths. Sixteen years of annual national data were available for cannabis potency, obtained through randomised sampling at the retail level, and quantitative analysis of key cannabinoids using internally audited and cross-validated laboratory methods. To our knowledge, these are the highest quality data available on long-term national trends in cannabis potency worldwide. The rise and fall of cannabis potency within the study period provide a unique opportunity to detect time-dependent associations in cannabis-related health outcomes. Official tolerance of cannabis use in the Netherlands minimises confounding influences of the criminal justice system and/or stigma. National drug treatment data provide a valid indicator of changes in burden and morbidity attributable to a particular substance, and were available annually from an internally-audited database. However, a key limitation is that these datasets were not linked at the individual level. Furthermore, data were not available at monthly or quarterly intervals, which could have improved the precision of statistical modelling. Prospective cohort data, using a comprehensive assessment of cannabis exposure including cannabis type (van der Pol *et al.*, 2013a) could allow associations to be tested within individuals and permit adjustment for other relevant confounds that could not be addressed in this study. However, data on cannabis potency is extremely rare in existing cohorts and we are unaware of any studies that have quantified THC concentrations in cannabis from the same individuals repeatedly over time. In order to provide the most reliable and valid estimates of users' exposure to variation in cannabis potency, we analysed samples of the most popular form of cannabis sold in the Netherlands (Niesink *et al.*, 2015, Schubart *et al.*, 2011, van der Pol *et al.*, 2013b, Van Laar *et al.*, 2016). We cannot exclude the possibility that any effects of potency might have been driven by use of other types of cannabis. However, similar trends in potency have been reported for other cannabis products over the same time period (Niesink *et al.*, 2015, Pijlman *et al.*, 2005) with no evidence for a product by time interaction (Niesink *et al.*, 2015). Prevalence data were available for both adolescent and adult cannabis use in the last month. However, these were not collected annually and were not linked to outcomes at the population level. This limits the extent to which prevalence can be excluded as a possible explanation for trends in cannabis treatment. However, the same (lack of) relationship has also been observed in other countries with annual data such as the UK, where prevalence of cannabis use has decreased, but potency and treatment admissions have both risen (Freeman and Winstock, 2015).

In conclusion, this sixteen-year observational study found positive associations between changes in cannabis potency and first-time cannabis admissions to specialist drug treatment. After adjusting for other drug treatment admissions and client demographics, these associations were attenuated but remained statistically significant at 5-7 year time lags. The strongest association, both before and after adjustment, was at 5 years. Our findings have relevance in the context of rising cannabis potency, increased demand for cannabis treatment, and global policy reform.

Acknowledgments

We would like to thank the Netherlands Ministry of Health, Welfare and Sport for their support.

Financial support

This study was funded by the Society for the Study of Addiction (Senior Academic Fellowship awarded to TF).

Conflict of interest

No authors have any potential conflicts of interest to declare.

References

Behrendt, S., Wittchen, H.-U., Höfler, M., Lieb, R. & Beesdo, K. (2009). Transitions from first substance use to substance use disorders in adolescence: is early onset associated with a rapid escalation? *Drug and alcohol dependence* 99, 68-78.

Brunt, T. M., van Laar, M., Niesink, R. J. & van den Brink, W. (2010). The relationship of quality and price of the psychostimulants cocaine and amphetamine with health care outcomes. *Drug and alcohol dependence* 111, 21-29.

Cascini, F., Aiello, C. & Di Tanna, G. (2012). Increasing delta-9-tetrahydrocannabinol (Δ-9-THC) content in herbal cannabis over time: systematic review and meta-analysis. *Current drug abuse reviews* 5, 32-40.

Chan, G. C., Hall, W., Freeman, T. P., Ferris, J., Kelly, A. B. & Winstock, A. (2017). User characteristics and effect profile of Butane Hash Oil: An extremely high-potency cannabis concentrate. *Drug and Alcohol Dependence* 178, 32-38.

Colizzi, M. & Bhattacharyya, S. (2017). Does Cannabis Composition Matter? Differential Effects of Delta-9-tetrahydrocannabinol and Cannabidiol on Human Cognition. *Current Addiction Reports* 4, 62-74.

Courtney, K. E., Mejia, M. H. & Jacobus, J. (2017). Longitudinal Studies on the Etiology of Cannabis Use Disorder: A Review. *Current Addiction Reports* 4, 43-52.

Curran, H. V., Freeman, T. P., Mokrysz, C., Lewis, D. A., Morgan, C. J. & Parsons, L. H. (2016). Keep off the grass? Cannabis, cognition and addiction. *Nature Reviews Neuroscience* 17, 293-306.

D'Souza, D. C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., Perry, E. & Krystal, J. (2008). Blunted psychotomimetic and amnestic effects of Δ-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology* 33, 2505-2516.
Di Forti, M., Marconi, A., Carra, E., Fraietta, S., Trotta, A., Bonomo, M., Bianconi, F., Gardner-Sood, P., O'Connor, J. & Russo, M. (2015). Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *The Lancet Psychiatry* 2, 233-238.
ElSohly, M. A., Mehmedic, Z., Foster, S., Gon, C., Chandra, S. & Church, J. C. (2016). Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. *Biological psychiatry* 79, 613-619.
EMCDDA (2014). Report to the EMCDDA by the Reitox National Focal Point. The Netherlands Drug Situation 2014.
EMCDDA (2016). European Drug Report. European Monitoring Centre for Drugs and Drug Addiction.
Englund, A., Freeman, T. P., Murray, R. M. & McGuire, P. (2017). Can we make cannabis safer? *The Lancet Psychiatry* 4, 643-648.
Freeman, T. & Winstock, A. (2015). Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychological medicine* 45, 3181-3189.
Freeman, T. P., Morgan, C. J. A., Hindocha, C., Schafer, G. L., Das, R. K. & Curran, H. V. (2014). Just say 'know': how do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints? *Addiction* 109, 1686-1694.
Freeman, T. P. & Swift, W. (2016). Cannabis potency: the need for global monitoring. *Addiction* 111, 376-377.
McLaren, J., Swift, W., Dillon, P. & Allsop, S. (2008). Cannabis potency and contamination: a review of the literature. *Addiction* 103, 1100-1109.
Meier, M. H. (2017). Associations between butane hash oil use and cannabis-related problems. *Drug and Alcohol Dependence* 179, 25-31.
Mokrysz, C., Freeman, T., Korkki, S., Griffiths, K. & Curran, H. (2016). Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males. *Translational Psychiatry* 6, e961.
Monaghan, M., Hamilton, I., Lloyd, C. & Paton, K. (2016). Cannabis matters? Treatment responses to increasing cannabis presentations in addiction services in England. *Drugs: Education, Prevention and Policy* 23, 54-61.
Monshouwer, K., Van Laar, M. & Vollebergh, W. A. (2011). Buying cannabis in 'coffee shops'. *Drug and Alcohol Review* 30, 148-156.
Montanari, L., Guarita, B., Mounteney, J., Zipfel, N. & Simon, R. (2017). Cannabis Use among People Entering Drug Treatment in Europe: A Growing Phenomenon? *European addiction research* 23, 113.
NDTMS (2014). Adult Drug Statistics from the National Drug Treatment Monitoring System (NDTMS)
Nguyen, H. & Reuter, P. (2012). How risky is marijuana possession? Considering the role of age, race, and gender. *Crime & Delinquency* 58, 879-910.
Niesink, R. J., Rigter, S., Koeter, M. W. & Brunt, T. M. (2015). Potency trends of Δ9-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005–15. *Addiction* 110, 1941-1950.
Pijlman, F., Rigter, S., Hoek, J., Goldschmidt, H. & Niesink, R. (2005). Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. *Addiction biology* 10, 171-180.
Potter, D. J., Clark, P. & Brown, M. B. (2008). Potency of Δ9–THC and other cannabinoids in cannabis in England in 2005: Implications for psychoactivity and pharmacology. *Journal of forensic sciences* 53, 90-94.

Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Ajnakina, O., Gayer-Anderson, C., Colizzi, M., Quattrone, D. & Behlke, I. (2016). Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. *The Lancet Psychiatry* 3, 947-953.
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* 130, 216-221.
Sevigny, E. L. (2013). Is today's marijuana more potent simply because it's fresher? *Drug testing and analysis* 5, 62-67.
Silins, E., Horwood, L. J., Patton, G. C., Fergusson, D. M., Olsson, C. A., Hutchinson, D. M., Spry, E., Toumbourou, J. W., Degenhardt, L. & Swift, W. (2014). Young adult sequelae of adolescent cannabis use: an integrative analysis. *The Lancet Psychiatry* 1, 286-293.
Smart, R., Caulkins, J. P., Kilmer, B., Davenport, S. & Midgette, G. (2017). Variation in cannabis potency and prices in a newly-legal market: Evidence from 30 million cannabis sales in Washington State. *Addiction* 112, 2167-2177.
Swift, W., Wong, A., Li, K. M., Arnold, J. C. & McGregor, I. S. (2013). Analysis of cannabis seizures in NSW, Australia: cannabis potency and cannabinoid profile. *PloS one* 8, e70052.
UNODC (2016). *United Nations Office on Drugs and Crime. World Drug Report*.
van der Pol, P., Liebregts, N., Brunt, T., Amsterdam, J., Graaf, R., Korf, D. J., Brink, W. & Laar, M. (2014). Cross-sectional and prospective relation of cannabis potency, dosing and smoking behaviour with cannabis dependence: an ecological study. *Addiction* 109, 1101-1109.
van der Pol, P., Liebregts, N., de Graaf, R., Korf, D. J., van den Brink, W. & van Laar, M. (2013a). Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study. *Drug and alcohol dependence* 133, 352-359.
van der Pol, P., Liebregts, N., Graaf, R., Have, M., Korf, D. J., Brink, W. & Laar, M. (2013b). Mental health differences between frequent cannabis users with and without dependence and the general population. *Addiction* 108, 1459-1469.
Van Laar, M., Van Der Pol, P. & Niesink, R. (2016). Limitations to the Dutch cannabis toleration policy: assumptions underlying the reclassification of cannabis above 15% THC. *International Journal of Drug Policy* 34, 58-64.
Wisselink, D. J., Kuijpers, W. G. T. & Mol, A. (2016). Key Figures Addiction Care 2015. Stichting Informatie Voorziening Zorg: Houten.
Wouters, M. & Korf, D. J. (2009). Access to licensed cannabis supply and the separation of markets policy in the Netherlands. *Journal of Drug Issues* 39, 627-651.

Table 1: Unstandardised regression coefficients (95% CIs) for associations between delta-9-tetrahydrocannabinol (THC) concentrations in domestic herbal cannabis and first-time cannabis admissions to drug treatment, at time lags of 0-10 years. Estimates are presented unadjusted (Model 1), adjusted for age and sex (Model 2), and adjusted for age, sex and first-time non-cannabis admissions (Model 3)

		Model 1 (unadjusted)				Model 2 (adjusted for age and sex)				Model 3 (adjusted for age, sex and non-cannabis admissions)			
Lag (years)	**df**	**b**	**95% CI**	**z**	***p***	**b**	**95% CI**	**z**	***p***	**b**	**95% CI**	**z**	***p***
0	1, 969	0.075	(0.028, 0.123)	3.113	0.0018	0.067	(0.041 0.092)	5.182	<0.0001	0.013	(-0.007 0.033)	1.300	0.1937
1	1, 909	0.139	(0.090, 0.189)	5.528	<0.0001	-0.054	(-0.078 -0.030)	-4.387	<0.0001	-0.039	(-0.061 -0.018)	-3.638	0.0003
2	1, 843	0.169	(0.118, 0.220)	6.514	<0.0001	-0.013	(-0.039 0.012)	-1.007	0.3140	-0.015	(-0.038 0.007)	-1.324	0.1856
3	1, 782	0.238	(0.185, 0.290)	8.895	<0.0001	0.015	(-0.014 0.044)	1.008	0.3136	-0.028	(-0.054 -0.002)	-2.142	0.0322
4	1, 724	0.287	(0.233, 0.341)	10.381	<0.0001	0.042	(0.012 0.072)	2.768	0.0056	0.014	(-0.013 0.041)	1.021	0.3073
5	1, 659	0.370	(0.317, 0.424)	13.666	<0.0001	0.095	(0.063 0.128)	5.793	<0.0001	0.082	(0.052 0.111)	5.428	<0.0001
6	1, 593	0.335	(0.289, 0.380)	14.450	<0.0001	0.051	(0.030 0.072)	4.719	<0.0001	0.037	(0.015 0.059)	3.286	0.0010
7	1, 537	0.213	(0.181, 0.245)	13.053	<0.0001	0.039	(0.018 0.061)	3.601	0.0003	0.044	(0.023 0.064)	4.213	<0.0001
8	1, 477	0.122	(0.089, 0.155)	7.237	<0.0001	-0.028	(-0.052 -0.004)	-2.245	0.0248	0.005	(-0.013 0.023)	0.581	0.5616
9	1, 424	0.094	(0.064, 0.123)	6.189	<0.0001	0.014	(-0.014 0.041)	0.980	0.3272	-0.000	(-0.018 0.018)	-0.025	0.9802
10	1, 366	0.017	(-0.009, 0.044)	1.274	0.2027	-0.027	(-0.051 -0.002)	-2.160	0.0308	-0.006	(-0.010 -0.002)	-2.767	0.0057

Figure 1: Mean (95% CI) concentrations of delta-9-tetrahydrocannabinol (THC) in domestic herbal cannabis and first-time cannabis admissions to specialist drug treatment (per 100,000 inhabitants) from 2000-2015