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Mental health differences between frequent cannabis users with and without dependence and the general population

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ABSTRACT

Aims To compare the prevalence of mental disorders between frequent cannabis users with and without dependence and the general population. Design Cross-sectional comparison of interview data. Setting Enriched community sample of frequent cannabis users and a representative sample of non-users and non-frequent users from the general population. Participants A total of 521 young adult (aged 18–30 years) frequent cannabis users, 252 of whom were with DSM-IV cannabis dependence (D+) and 269 without DSM-IV cannabis dependence (D−), and 1072 young adults from the general population. Measurements Multinomial logistic regression was used to compare groups regarding the presence of DSM-IV mental disorders. Detailed measures of cannabis use, childhood adversity and other substance use were considered confounders. Findings Compared with the general population, externalizing disorders were more prevalent in D− [odds ratio (OR) = 8.91, P < 0.001] and most prevalent in D+ (OR = 17.75, P < 0.001), but internalizing disorders were associated only with D+ (mood OR = 4.15, P < 0.001; anxiety OR = 2.20, P = 0.002). Associations were attenuated (and often became non-significant) after correction for childhood adversity and substance use other than cannabis. However, the prevalence of mental disorders remained higher in D+ compared with D− (OR = 2.40, P < 0.001), although cannabis use patterns were remarkably similar. Conclusions Cannabis use patterns, childhood adversity and the use of other substances are similar in dependent and non-dependent frequent cannabis users. With the exception of more externalizing disorders, the mental health condition of non-dependent frequent cannabis users is similar to that of the general population, whereas it is worse in dependent frequent cannabis users.

Keywords Dependence, frequent cannabis use, general population, mental disorders.

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INTRODUCTION

Both frequent (daily or nearly daily) cannabis use and cannabis dependence are associated with various mental health problems [1–7]. However, in most studies the overlap (an estimated 20–50% [8,9]) between dependent users and frequent users is ignored [1–5,10–16]. Associations between mental health problems and non-dependent frequent use are therefore unknown. As a consequence, the mental health risks based on studies of all frequent users together may be overestimated, because the subgroup of dependent frequent users may magnify this association.

Most information on the association between frequent or dependent cannabis use and mental disorders is derived from general population studies. These studies show higher rates of depression and anxiety in dependent versus non-dependent users and in heavy versus infrequent users [3,6,10–16]. However, other studies found similar rates of internalizing disorders in heavy and infrequent users [6,17–19]. On one hand, these inconsistent findings may be due to small sample size, imprecise and
Inconsistent measurement of cannabis use or divergence in measures of mood and anxiety problems and disorders [10,11]. On the other hand, they may indicate a variation in the percentages of dependent users, suggesting that associations between internalizing disorders and heavy use without dependence are small.

More robust associations were found between externalizing disorders and both cannabis use and dependence, especially with regard to attention deficit and hyperactivity disorder (ADHD) and conduct disorder (CD) [12,14,20,21]. Nevertheless, as general population studies either investigate frequency of use or dependence, a direct comparison between frequent cannabis users with and without dependence is lacking. Moreover, general population studies do not allow a comparison between non-dependent frequent users and the general population. Therefore, it remains unknown to what extent the presence of specific internalizing and externalizing mental disorders differs between dependent and non-dependent frequent users and the general population.

To our knowledge, there is only one study on differences in mental health between dependent and non-dependent frequent cannabis users [22]. In this convenience sample (using mailing lists of organizations committed to altering drug laws), dependent frequent cannabis users reported higher 'levels of depression' than non-dependent frequent users. In addition, dependent users were significantly younger, less educated and, although both groups were daily users, dependent users reported feeling 'higher' on average during cannabis consumption, used more joints weekly and more often used other substances. However, these results were derived from a web-based survey, using proxy measures of dependence and depression, rather than valid standardized instruments measuring (DSM-IV) diagnoses.

Use of other drugs has been related to both mental health problems and cannabis use or dependence, and attenuates these associations [5,7,23–26]. This is also true for childhood adversities [27,28]. In particular, it has been suggested that the development of cannabis abuse and dependence symptoms are influenced by childhood maltreatment both directly and through the development of externalizing (but not internalizing) disorders [29]. Although these factors do not negate mental health differences, they should be considered as alternative explanatory factors for mental health differences between these groups.

Moreover, some investigators have suggested that a detailed assessment of cannabis exposure could improve our understanding of its association with mental disorders [30–32]. Usage patterns may vary widely—also among frequent users. Hence, exposure may vary from one joint several days per week to daily consumption of numerous joints with a high dose of very potent cannabis. However, most studies measure only frequency of use, sometimes complemented with the number of units (often joints) per day, and neglect differences in dose per joint, cannabis potency and type (marijuana or hashish). Other cannabis factors shown to differ between dependent and non-dependent users that may also be associated with mental health problems include setting of use (e.g. solitary use and time of use) [33] and motives for cannabis use [34,35]. In particular, using cannabis to cope with negative affect has been identified as a mediator between dependence and internalizing disorders [36].

General population studies mainly ignore the distinction between dependent and non-dependent frequent cannabis use. Therefore, the primary aim of the present study was to compare the presence of DSM-IV mental disorders in three groups: young adult dependent frequent cannabis users, young adult non-dependent frequent cannabis users and young adult subjects from the general population. In these respective populations, a decreasing gradient in the prevalence of mental disorders was hypothesized [5,37]. Childhood adversity and substance use were expected to attenuate the mental health differences between the three groups.

The second aim was to investigate whether differences in cannabis use patterns and habits, assessed in detail in dependent and non-dependent frequent users, may explain mental health differences between both user groups. It was hypothesized that dependent users would exhibit higher levels of cannabis exposure and more risky consumption habits [22] and that these factors would explain, at least partially, the mental health differences between the two groups.

**METHODS**

**Subjects**

Data on frequent dependent and non-dependent cannabis users were gathered from the baseline wave of a cohort study on predictors of transitions in frequent cannabis use and dependence (CanDep). For a detailed description of the study design see Van der Pol et al. [38]. In brief, 600 cannabis users were recruited from ‘coffee shops’ and through chain referral between September 2008 and April 2009. Most Dutch cannabis users buy cannabis in designated coffee shops, where the sale and use of small amounts of cannabis are officially tolerated [39]. Inclusion was restricted to those aged 18–30 years who used cannabis on 3 or more days per week for the past 12 months. Dependent frequent cannabis users (n = 252) were distinguished from non-dependent frequent cannabis users (n = 348) based on the 12-month DSM-IV diagnosis of cannabis dependence at baseline.
according to the Composite International Diagnostic Interview (CIDI) 3.0 (see below). Seventy-eight of the 348 frequent cannabis users without a 12-month diagnosis of cannabis dependence had a life-time diagnosis of dependence. They were excluded from the analyses because their inclusion might attenuate the differences between groups.

Data on the general population were derived from a Dutch representative psychiatric-epidemiological general population survey, NEMESIS-2 (Netherlands Mental Health Survey and Incidence Study-2) [38,40]. Through a multi-stage, stratified random sampling procedure, 6646 participants between the ages of 18 and 64 years were recruited between November 2007 and July 2009. There were 1118 respondents aged 18–30 years, of whom 24 were excluded because they had used cannabis frequently (≥3 days per week for the past 12 months), but lacked the detailed cannabis exposure assessment allowing them to be included in the CanDep sample. Twenty-two NEMESIS-2 respondents who completed an abbreviated interview without childhood and substance use variables were excluded, as well as one CanDep respondent with missing data regarding the presence of mental disorders. The total sample comprised 1593 participants: 521 from the CanDep study (252 dependent and 269 non-dependent frequent cannabis users) and 1072 non-users and non-frequent users from NEMESIS-2.

Instruments and assessments

Measures in the CanDep and NEMESIS-2 samples converged to a large extent: they included the CIDI 3.0 for diagnoses of mental disorders and additional scales, which are discussed in detail in Van der Pol et al. [38]. Data were collected through comprehensive face-to-face computer-assisted interviews conducted by trained lay interviewers. The interviews took place at the participant’s home (29.4%), the research institute (20.7%), in a coffee shop (12.9%), in a café (23.0%) or a public venue such as a park or library (14.0%). The choice of location was made to suit the participant, as long as a confidential conversation was feasible. The interview required the participants to be fluent in Dutch.

Socio-demographic factors

Socio-demographic variables shown empirically to influence cannabis dependence included the following: sex, age, ethnicity (western/non-western), educational level (primary or lower secondary/higher secondary/higher professional/university), urbanicity (urban/rural), employment situation (employed/unemployed or unable to work/student) and living arrangements (living alone/with others) [7,12,26].

Mental disorders

The following DSM-IV 12-month diagnoses were assessed with the CIDI 3.0: cannabis dependence, major depression, bipolar disorder, dysthymia, social phobia, panic disorder, generalized anxiety disorder, agoraphobia and adult ADHD. In addition, antisocial personality disorder (ASP), childhood ADHD and CD were assessed with the CIDI 3.0.

Childhood adversities

Participants were asked if they had experienced the following life events before the age of 16 years: being from a single-parent family, parental divorce and parental death. Additionally, using a list of examples, participants were asked whether they had experienced emotional, psychological, physical and/or sexual abuse [27,41,42]. The examples included parental ignorance of one’s problems and experiences, being subordinated to siblings, being beaten up or being touched or having to touch someone in a sexual way. This instrument has been employed in numerous studies [43–45]. As these experiences may not always occur in isolation, the cumulative number of these seven childhood adversities was also reported.

Substance use

For all participants, age of onset and use in the past 12 months were assessed for cannabis, ecstasy (XTC), cocaine and (weekly or more frequent) alcohol use.

Cannabis use patterns and habits

Detailed cannabis use was assessed in the CanDep sample and included the self-reported number of cannabis use days in the past 4 weeks, number of joints per typical cannabis use day, preferred cannabis type (marijuana/hashish/no preference), subjective estimates of preferred cannabis potency (low/middle/high), average level of intoxication during cannabis consumption on a 1–10 visual analogue scale, dosage of cannabis per joint based on the estimated number of joints made from 1 g of cannabis, cannabis use location (home/coffee shop/non-selective) and solitary use most of the time (yes/no). Information on timing of use included a dichotomous assessment of using [also] on weekdays and [also] in daytime, and the estimated average number of hours ‘high’ on a cannabis using day. Furthermore, age of onset of regular use (at least once monthly) was assessed.

Motives for cannabis use

In the CanDep sample, motives for cannabis use were assessed with the Marijuana Motives Measure (MMM)
This 25-item questionnaire consists of five internally consistent subscales: enhancement (e.g. "because it is exciting"); Cronbach’s $\alpha = 0.66$, conformity (e.g. "to fit in with the group I like"); $\alpha = 0.74$, expansion (e.g. "to expand my awareness"); $\alpha = 0.85$, coping (e.g. "to forget my worries"); $\alpha = 0.85$ and social (e.g. "because it makes social gatherings more fun"); $\alpha = 0.75$.

Analysis

Socio-demographic factors were compared for non-dependent cannabis users, dependent cannabis users and the general population in a multi-variable multinomial logistic regression model with the grouping variable as dependent variable. The general population was used as the reference. To allow comparison between dependent and non-dependent frequent users, non-dependent users were also defined as the reference group in the same models.

This multinomial logistic regression procedure was also used to compare 12-month mental disorders between the three groups. Similarly, childhood adversity and substance use were compared. Next, comparisons of mental health between all three groups were adjusted for the number of childhood adversity factors and current substance use (tobacco, alcohol, illicit substances) [23, 42].

Similarly, dependent and non-dependent frequent cannabis users were compared regarding detailed measures of cannabis use (exposure, setting and motives for use) with logistic regression. Mental health in these two groups was then compared—adjusted for cannabis use variables that differed between the CanDep samples.

All analyses were computed in STATA version 11.1 and were adjusted for socio-demographic factors. STATA produces relative risk ratios in multinomial regression analyses, which can be interpreted as odds ratios (ORs) [47]. The NEMESIS-2 data were weighted to be representative for the general Dutch population. Moreover, multiplication of participants with similar characteristics is a risk of both chain referral (CanDep) and stratified samples based on municipalities (NEMESIS-2). Therefore, analyses allowed for clustering within CanDep chains of referral and within NEMESIS-2 municipalities. To account for multiple comparisons, a $P$-value $\leq 0.005$ was considered statistically significant. As missing data were limited, complete case analyses were employed (itemized missing values are reported in footnotes to the Tables).

RESULTS

Socio-demographics

No statistically significant (multivariate) differences in socio-demographic variables were observed between dependent and non-dependent users (Table 1) [38]. However, both groups were very different from the general population sample, except for living alone.

Mental disorders

Compared to the general population sample, both dependent and non-dependent frequent cannabis users were at higher risk of having ‘any mental disorder’ (Table 1). However, the risk was significantly and substantially higher for dependent (OR = 14.97, $P < 0.001$) than non-dependent users (OR = 5.35, $P < 0.001$). Analysis of specific disorders showed that non-dependent frequent users were only at significantly higher risk of having externalizing, not internalizing disorders. In contrast, dependent cannabis users showed higher risk of having both internalizing and externalizing disorders. Besides the higher risk of ADHD in frequent cannabis users compared to the general population, additional analyses showed that frequent cannabis users also had higher persistency rates into adulthood (91% versus 70% persistence; OR = 10.1, $P = 0.007$).

Dependent frequent users had mental disorders more often than non-dependent cannabis users, both internalizing as well as (childhood and adult) externalizing disorders (Table 1). CD and ASP were the most prevalent disorders in both groups but, overall, ORs were larger for internalizing compared to externalizing disorders.

Childhood and substance use

Several potential confounders for mental health differences were considered. Generally, both frequently using groups experienced more childhood adversity and used more substances than the general population sample. However, the loss of parent(s) and childhood sexual abuse did not differ (Table 1). Moreover, frequent cannabis users reported less weekly (or more frequent) alcohol use than the general population sample. Remarkably, the frequently using groups were mostly similar, although dependent users reported use of XTC or cocaine and a history of childhood physical abuse more often compared to non-dependent frequent cannabis users.

After adjustment for these variables, patterns in associated mental disorders changed considerably in the

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1Matching was considered, but socio-demographic characteristics of the samples did not allow this strategy. As the CanDep sample was young and mainly male, there were insufficient males in their early 20s in the NEMESIS-2 sample. Therefore, all analyses were adjusted statistically for socio-demographic variables.

2Odds ratios of continuous variables represent the percentage increase in the odds of being in one versus the reference population; e.g. for every year a frequent user has used cannabis, the probability to be dependent increases with 11% (Table 3).
Table 1 Comparison between dependent and non-dependent frequent cannabis users and the general population: socio-demographic variables, 12-month disorders, childhood adversity, and substance use.

<table>
<thead>
<tr>
<th></th>
<th>N2*</th>
<th>D−</th>
<th>D+</th>
<th>D− versus N2</th>
<th>D+ versus N2</th>
<th>D+ versus D−</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>OR, P</td>
<td>OR, P</td>
</tr>
<tr>
<td>Male</td>
<td>464</td>
<td>48.7</td>
<td>206</td>
<td>76.6</td>
<td>200</td>
<td>79.4</td>
</tr>
<tr>
<td>Mean age (SE)</td>
<td>24.0(0.16)</td>
<td>21.9(0.23)</td>
<td>22.1(0.24)</td>
<td>0.78&lt;0.001</td>
<td>0.81&lt;0.001</td>
<td>1.040.29</td>
</tr>
<tr>
<td>Western (versus non-western)</td>
<td>973</td>
<td>88.0</td>
<td>184</td>
<td>68.4</td>
<td>188</td>
<td>74.6</td>
</tr>
<tr>
<td>Education primary/secondary</td>
<td>208</td>
<td>34.0</td>
<td>81</td>
<td>30.1</td>
<td>67</td>
<td>26.6</td>
</tr>
<tr>
<td>Higher secondary</td>
<td>441</td>
<td>42.6</td>
<td>104</td>
<td>38.7</td>
<td>95</td>
<td>37.7</td>
</tr>
<tr>
<td>Higher professional</td>
<td>423</td>
<td>23.4</td>
<td>84</td>
<td>31.2</td>
<td>90</td>
<td>35.7</td>
</tr>
<tr>
<td>Employment employed</td>
<td>732</td>
<td>65.4</td>
<td>122</td>
<td>45.4</td>
<td>88</td>
<td>34.9</td>
</tr>
<tr>
<td>Student</td>
<td>268</td>
<td>27.3</td>
<td>114</td>
<td>42.4</td>
<td>121</td>
<td>48.0</td>
</tr>
<tr>
<td>Unemployed/unable to work</td>
<td>72</td>
<td>7.3</td>
<td>33</td>
<td>12.3</td>
<td>43</td>
<td>17.1</td>
</tr>
<tr>
<td>Living alone (versus with others)</td>
<td>273</td>
<td>18.3</td>
<td>54</td>
<td>20.1</td>
<td>53</td>
<td>21.0</td>
</tr>
<tr>
<td>Urban (versus town/village)</td>
<td>542</td>
<td>55.2</td>
<td>247</td>
<td>91.8</td>
<td>236</td>
<td>93.7</td>
</tr>
<tr>
<td>Any 12-month disorder</td>
<td>184</td>
<td>19.7</td>
<td>146</td>
<td>54.3</td>
<td>189</td>
<td>75.0</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>72</td>
<td>8.0</td>
<td>17</td>
<td>6.3</td>
<td>46</td>
<td>18.3</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>57</td>
<td>5.6</td>
<td>11</td>
<td>4.1</td>
<td>30</td>
<td>11.9</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>14</td>
<td>2.3</td>
<td>6</td>
<td>2.2</td>
<td>16</td>
<td>6.4</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>8</td>
<td>0.9</td>
<td>2</td>
<td>0.7</td>
<td>7</td>
<td>2.8</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>72</td>
<td>7.1</td>
<td>11</td>
<td>4.1</td>
<td>38</td>
<td>15.1</td>
</tr>
<tr>
<td>Social phobia</td>
<td>45</td>
<td>4.5</td>
<td>7</td>
<td>2.6</td>
<td>27</td>
<td>10.7</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>14</td>
<td>1.1</td>
<td>2</td>
<td>0.7</td>
<td>12</td>
<td>4.8</td>
</tr>
<tr>
<td>General anxiety disorder</td>
<td>25</td>
<td>2.4</td>
<td>2</td>
<td>0.7</td>
<td>8</td>
<td>3.2</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>3</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>Adult ADHD</td>
<td>34</td>
<td>4.5</td>
<td>43</td>
<td>16.0</td>
<td>84</td>
<td>33.3</td>
</tr>
<tr>
<td>Any childhood disorder</td>
<td>73</td>
<td>9.3</td>
<td>120</td>
<td>44.6</td>
<td>147</td>
<td>58.3</td>
</tr>
<tr>
<td>Childhhold ADHD</td>
<td>30</td>
<td>3.2</td>
<td>20</td>
<td>7.4</td>
<td>35</td>
<td>13.9</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>54</td>
<td>7.9</td>
<td>113</td>
<td>42.0</td>
<td>142</td>
<td>56.4</td>
</tr>
<tr>
<td>Number childhood adversities (SE)</td>
<td>1.52 (0.04)</td>
<td>2.07 (0.08)</td>
<td>2.40 (0.10)</td>
<td>1.66&lt;0.001</td>
<td>2.11&lt;0.001</td>
<td>1.270.006</td>
</tr>
<tr>
<td>Not raised by both parents</td>
<td>90</td>
<td>9.5</td>
<td>68</td>
<td>25.3</td>
<td>68</td>
<td>27.0</td>
</tr>
<tr>
<td>Parents divorced</td>
<td>184</td>
<td>19.2</td>
<td>97</td>
<td>36.3</td>
<td>96</td>
<td>38.1</td>
</tr>
<tr>
<td>Loss of parent(s)</td>
<td>38</td>
<td>3.8</td>
<td>22</td>
<td>8.2</td>
<td>23</td>
<td>9.1</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>124</td>
<td>11.9</td>
<td>73</td>
<td>27.1</td>
<td>96</td>
<td>38.1</td>
</tr>
<tr>
<td>Psychological abuse</td>
<td>174</td>
<td>14.8</td>
<td>105</td>
<td>39.0</td>
<td>119</td>
<td>47.2</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>73</td>
<td>6.4</td>
<td>40</td>
<td>14.9</td>
<td>68</td>
<td>27.0</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>63</td>
<td>6.1</td>
<td>17</td>
<td>6.3</td>
<td>19</td>
<td>7.5</td>
</tr>
<tr>
<td>Last month tobacco use</td>
<td>362</td>
<td>34.4</td>
<td>211</td>
<td>78.4</td>
<td>211</td>
<td>83.7</td>
</tr>
<tr>
<td>12-month weekly–daily alcohol use</td>
<td>662</td>
<td>63.1</td>
<td>129</td>
<td>48.0</td>
<td>128</td>
<td>50.8</td>
</tr>
<tr>
<td>12-month cocaine or XTC use</td>
<td>39</td>
<td>3.8</td>
<td>112</td>
<td>41.6</td>
<td>149</td>
<td>59.1</td>
</tr>
</tbody>
</table>

D+ frequent cannabis users with 12-month cannabis dependence (n = 252); D− frequent cannabis users who have never fulfilled criteria for cannabis dependence (n = 269); N2 non-users and non-frequent users in the general population (n = 1072). N2 percentages weighted to be representative for the general Dutch population. Odds ratios (OR) are adjusted for the socio-demographic factors. In bold type, P < 0.005. Two cases had missing values for both last month tobacco use and parental divorce. XTC: ecstasy.
comparison with the general population (Table 2). Only the risk of having CD remained significantly higher for both dependent and non-dependent users compared to the general population sample, and dependent users had a higher risk of panic disorder. The confounders (childhood adversities and substance use) contributed equally to these attenuating effects (data not shown).

By contrast, patterns in the associations remained similar in the adjusted comparison of frequent users with and without dependence, although ORs were attenuated (Table 2). Significant differences included the major diagnostic categories (any disorder, any mood disorder, any anxiety disorder, any childhood disorder), ASP and CD.

### DISCUSSION

This is, to our knowledge, the first study to consider the distinction between dependent and non-dependent frequent cannabis users in a comparison of DSM-IV mental disorders with the general population. The mental health of non-dependent frequent cannabis users was better than expected from studies of all (including dependent) frequent users [3,10–16,20]; although mental disorders were more common in non-dependent users than in the general population (OR = 5.35, P < 0.001), this was largely attributable to (childhood) externalizing disorders (OR = 8.91, P < 0.001), whereas there was no difference in the presence of internalizing disorders. Dependent users had a higher risk of panic disorder. The confounders (childhood adversities and substance use) contributed equally to these attenuating effects (data not shown).

### Table 2 Adjusted comparison of 12-month disorders between dependent and non-dependent frequent cannabis users and the general population.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OR</th>
<th>P</th>
<th>OR</th>
<th>P</th>
<th>OR</th>
<th>P</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any 12-month disorder</td>
<td>2.21</td>
<td>&lt;0.001</td>
<td>5.30</td>
<td>&lt;0.001</td>
<td>2.40</td>
<td>&lt;0.001</td>
<td>2.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>0.55</td>
<td>0.26</td>
<td>1.62</td>
<td>0.34</td>
<td>2.93</td>
<td>0.002</td>
<td>2.67</td>
<td>0.003</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>1.09</td>
<td>0.87</td>
<td>2.81</td>
<td>0.08</td>
<td>2.58</td>
<td>0.04</td>
<td>2.22</td>
<td>0.08</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>0.28</td>
<td>0.06</td>
<td>0.80</td>
<td>0.68</td>
<td>2.85</td>
<td>0.06</td>
<td>2.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>7.23</td>
<td>0.05</td>
<td>19.81</td>
<td>0.01</td>
<td>2.74</td>
<td>0.28</td>
<td>2.70</td>
<td>0.18</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>0.32</td>
<td>0.009</td>
<td>1.12</td>
<td>0.79</td>
<td>3.55</td>
<td>&lt;0.001</td>
<td>2.95</td>
<td>0.004</td>
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<tr>
<td>Social phobia</td>
<td>0.38</td>
<td>0.11</td>
<td>1.53</td>
<td>0.49</td>
<td>4.00</td>
<td>0.007</td>
<td>3.25</td>
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<td>Panic disorder</td>
<td>1.48</td>
<td>0.56</td>
<td>9.13</td>
<td>&lt;0.001</td>
<td>6.16</td>
<td>0.009</td>
<td>4.87</td>
<td>0.01</td>
</tr>
<tr>
<td>General anxiety disorder</td>
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<td>0.03</td>
<td>0.58</td>
<td>0.54</td>
<td>3.61</td>
<td>0.20</td>
<td>2.84</td>
<td>0.28</td>
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<tr>
<td>Agoraphobia</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult ADHD</td>
<td>1.81</td>
<td>0.27</td>
<td>3.34</td>
<td>0.03</td>
<td>1.85</td>
<td>0.03</td>
<td>1.70</td>
<td>0.05</td>
</tr>
<tr>
<td>ASP</td>
<td>1.29</td>
<td>0.58</td>
<td>3.13</td>
<td>0.009</td>
<td>2.43</td>
<td>&lt;0.001</td>
<td>2.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any childhood disorder</td>
<td>3.90</td>
<td>&lt;0.001</td>
<td>6.86</td>
<td>&lt;0.001</td>
<td>1.76</td>
<td>0.002</td>
<td>1.72</td>
<td>0.008</td>
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<tr>
<td>Childhood ADHD</td>
<td>0.97</td>
<td>0.95</td>
<td>1.76</td>
<td>0.28</td>
<td>1.82</td>
<td>0.03</td>
<td>1.75</td>
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<td>Conduct disorder</td>
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<td>&lt;0.001</td>
<td>7.60</td>
<td>&lt;0.001</td>
<td>1.85</td>
<td>0.001</td>
<td>1.86</td>
<td>0.003</td>
</tr>
</tbody>
</table>

D+ frequent cannabis users with 12-month diagnosis of cannabis dependence (n = 252); D− frequent cannabis users who have never fulfilled criteria for cannabis dependence (n = 269); N2 non-users and non-frequent users in the general population (n = 1072). In bold type, P < 0.005. Model 1 was adjusted for socio-demographic factors, the number of childhood adversity factors, past month tobacco use, 12-month weekly alcohol use and 12-month cocaine or ecstasy use. The two cases with missing values (tobacco/divorce) were excluded. Model 2 included socio-demographic factors and statistically significant cannabis use differences between D+ and D− (Table 3: solitary use, expansion and coping motive). ADHD: attention deficit hyperactivity disorder; OR: odds ratio.
frequent cannabis users also had more mental disorders than the general population (OR = 14.97, \( P < 0.001 \)), but this was true for both internalizing disorders (mood OR = 4.15, \( P < 0.001 \); anxiety OR = 2.20, \( P = 0.002 \)) and externalizing disorders (any childhood OR = 17.75, \( P < 0.001 \); adult ADHD OR = 7.26, \( P < 0.001 \); ASP OR = 9.98, \( P < 0.001 \)). Moreover, cannabis use patterns and usage habits were compared thoroughly for frequent users with and without dependence and were found to be strikingly similar, with little effect on mental health differences.

**Limitations**

While an enriched population sample was recruited from coffee shops and through chain referral to achieve a large sample of frequent dependent and non-dependent cannabis users, this design cannot guarantee full representation of this population. Nonetheless, this does not necessarily mean that the sample is highly biased. After all, most frequent cannabis users in the Netherlands visit coffee shops, which is why recruitment occurred at these sites. Another issue that should be noted when interpreting the results is that all measures were based on self-report. While self-report has been accepted as a suitable method for obtaining information about population behaviours, over- or under-reporting due to deliberate concealment or unconscious memory effects cannot be precluded [38,48,49].

### Mental disorders

Roughly half the frequent users had an externalizing disorder. Compared to the general population, associations were strong in both groups, consistent with previous studies on externalizing disorders [12,14,21]. However, the association between CD and dependence was much stronger than reported previously (OR = 19.99, 0.001).
P < 0.001), due possibly to the higher frequency of cannabis use in the present study. CD and childhood ADHD usually precede cannabis initiation, and both disorders predict cannabis use and cannabis dependence [50,51]. Therefore, this finding emphasizes the potential of targeted prevention in this high-risk group, as well as the importance of treating these childhood disorders to reduce the development of both frequent cannabis use and dependence. This need is supported further by the greater persistence of ADHD into adulthood in frequent (dependent) cannabis users compared to the general population.

Internalizing disorders were associated only with dependent frequent use (adjusted for socio-demographic factors). This supports findings of a higher prevalence of internalizing disorders in dependent compared to non-dependent users in populations of daily cannabis users [22] and among less frequent (≥5 times last year) users [5]. However, in the latter study prevalence rates of mood disorders were comparable for dependent and non-dependent users, but higher than in non-users (<5 times) [5]. Overall, clinical practice should be alert to the comorbidity of cannabis dependence and internalizing disorders. Dependent cannabis users should be monitored for emerging symptoms of an internalizing disorder and vice versa. Timely intervention could prevent the onset of a secondary disorder [52], which is often associated with higher treatment costs and special treatment needs [53].

Childhood adversity and substance use

Frequent users with and without dependence were very similar with regard to childhood adversity and substance use, and both user groups scored much higher on these variables than the general population. These considerable differences between frequent cannabis users and the general population were responsible for the attenuation of most of the mental health differences between the user groups and the general population sample, most prominently regarding the high prevalence of internalizing disorders in dependent frequent users. Based on the assumed chronology, one may suggest that childhood adversity is partly responsible for the co-occurrence of cannabis dependence and mental disorders later in life [29]. However, compared to the general population, non-dependent users also had more childhood adversity without a higher risk of internalizing disorders. Therefore, other unmeasured factors are probably involved in the mental health differences between frequent users with and without dependence, such as personality, genetic vulnerability or other environmental factors [e.g. 54,55]. The same reasoning applies to the current use of other substances, but implications are less straightforward because the chronology assumption is much weaker. Therefore, the actual direction of associations remains unknown in this cross-sectional study.

Cannabis use in dependent and non-dependent frequent users

Remarkably, frequent users with and without dependence did not differ in cannabis exposure. Age of onset of (regular) cannabis use, frequency of cannabis use, preferred potency, number of joints, number of hours ‘high’ on a cannabis-using day, dosage per joint, potency preference or subjective achieved ‘high’ were all similar. This is inconsistent with the only other study comparing non-dependent and dependent frequent cannabis users, which showed higher levels of cannabis exposure in dependent daily users [22]. The fact that CanDep included respondents with a wider range in frequency of use cannot explain these contrasting results, as no difference in cannabis use patterns was observed in the daily cannabis users in our sample. However, the larger difference in number of joints per day between dependent and non-dependent users found by Looby et al. (0.35 joints compared to 0.2 joints in the current study) may actually correspond to similar delta9-tetrahydrocannabinol (THC) exposure, considering that the concentration of THC in Dutch marijuana is, on average, twice as high as Australian marijuana [56,57]). An alternative explanation could be that the differences in cannabis use between the non-dependent and dependent daily cannabis users in the study by Looby et al. were significant, but that the effect sizes were all somewhat small (standardized effect sizes ranging from 0.17 to 0.27), and that our study was not able to detect these small (clinically irrelevant) differences.

In contrast to the findings for cannabis use patterns, solitary use as well as (especially coping) motives for cannabis use discriminated between dependent and non-dependent frequent users. This finding is consistent with previous research in smaller samples of less frequent cannabis users [34,35,36,58]. These studies also suggested that coping motives moderate the association between internalizing disorders and cannabis dependence. This issue will be addressed in more detail in future studies of the CanDep cohort. However, after controlling for these differences in consumption habits and motives, dependent frequent cannabis users still showed a significantly higher prevalence of mental disorders compared to non-dependent frequent cannabis users, suggesting that other (vulnerability) factors are responsible for these mental health differences between the two cannabis user groups. These results also suggest that, rather than cannabis exposure, factors discriminating dependent from non-dependent frequent cannabis users include the presence of (pre-existing) mental disorders, solitary use and (coping) motives for cannabis use. This runs contrary to
the conclusion of Looby et al., that [daily] cannabis users should be informed that increased cannabis consumption is likely to produce or exacerbate many problems and undesirable mood states.

CONCLUSIONS

Our data suggest that the prevalence of internalizing disorders is no higher in non-dependent frequent cannabis users than in the general population, suggesting that the mental health risks of frequent non-dependent cannabis use may have been overestimated in previous studies. This observation may lead to an important nuance for public debate, policy discussions and prevention messages. However, non-dependent users had more externalizing disorders than the general population (but less than dependent users), both in childhood and adulthood. As these disorders are likely to precede cannabis use, this finding points to the potential of targeted prevention, early detection and treatment of children with externalizing disorders. It should be noted, however, that non-dependent users are still at risk of becoming dependent, and may therefore have a higher risk of internalizing disorders. Future studies should appreciate the distinction between dependent and non-dependent frequent users to investigate further whether the overlap between dependent and frequent cannabis users explains inconsistent findings regarding internalizing disorders.

Finally, frequent users with and without dependence had very similar cannabis use patterns and habits. Moreover, adjusting for the few differences in solitary use and motives for use did not eliminate the mental health differences between these groups of frequent cannabis users. Therefore, other unmeasured factors besides the currently studied cannabis use patterns and habits, childhood adversity and other substance use need to be examined to understand more clearly the reasons for the higher prevalence of mental disorders among dependent compared to non-dependent frequent cannabis users.

Declarations of interest

None.

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