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Evaluating the relationship between cannabis use and IQ in youth and young adults at clinical high risk of psychosis

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ABSTRACT

Among people with psychosis, those with a history of cannabis use show better cognitive performance than those who are cannabis naïve. It is unknown whether this pattern is present in youth at clinical high risk (CHR) of psychosis. We evaluated relationships between IQ and cannabis use while controlling for use of other substances known to impact cognition in 678 CHR and 263 healthy control (HC) participants. IQ was estimated using the Vocabulary and Block Design subtests of the Wechsler Abbreviated Scale of Intelligence. Drug and alcohol use severity and frequency were assessed with the Alcohol and Drug Use Scale, and we inquired participants' age at first use. CHR were further separated into early and late age at onset of cannabis use sub-groups, and low-, moderate- and high-frequency sub-groups. No significant differences in IQ emerged between CHR or HC cannabis users vs. non-users, or between use frequency groups. CHR late-onset users showed significantly higher IQ than CHR early-onset users. Age at onset of cannabis use was significantly and positively correlated with IQ in CHR only. Results suggest that age at onset of cannabis may be a more important factor for IQ than use current use or use frequency in CHR.

1. Introduction

Cannabis is the most widely used illicit substance in both schizophrenia and in those at clinical high risk (CHR) of developing psychosis (Addington et al., 2014). Furthermore, cannabis use severity is associated with greater positive symptoms in CHR (Caspi et al., 2005; Moore et al., 2007; Kuepper et al., 2011; Fusar-Poli et al., 2012) and epidemiological data suggest a role for cannabis in the onset of psychosis (Arseneault et al., 2002). Recent prospective data in CHR individuals have indicated that among lifetime cannabis users, higher baseline use severity (Buchy et al., 2015a), frequency (Valmaggia et al., 2014) and first use before the age of 15 (Arseneault et al., 2002; Valmaggia et al., 2014) are associated with an increased rate of conversion to psychosis.

It is well documented that among people diagnosed with a psychotic disorder, those with a history of cannabis use show better cognitive performance than those who are cannabis naïve (Potvin et al., 2008; Rabin et al., 2011; Yucel et al., 2012). A recent meta-analysis (Rabin et al., 2011) excluded studies with people with a current comorbid diagnosis of drug abuse and reported a medium effect size (Cohen's $d=0.48$) for higher IQ in cannabis-using individuals with schizophrenia compared to non-users. Stratifying patients according to cannabis use frequency has suggested higher IQ in low- vs. high-frequency users (Leeson et al., 2012), although another study failed to observe this relationship

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(Tosato et al., 2013). Yucel et al. (2012) did not observe differences in IQ in psychosis patients with a lifetime exposure to cannabis compared to never-users, or in users with an early vs. late age at onset of cannabis use. Thus there is some evidence that patients with psychosis with a positive lifetime exposure to cannabis and/or who are current users show higher IQ than abstinent patients, and that use frequency may associate with IQ. The relationship between IQ and age at onset of cannabis use in people with psychoses is less clear. No published studies have characterized IQ in youth at CHR of psychosis who use cannabis compared to those who do not.

Several explanations have been proposed to explain the higher cognitive abilities in cannabis-using vs. abstinent patients with schizophrenia. One suggestion is that among people who develop a psychosis, those who have used cannabis have better cognitive functioning because they have fewer neurodevelopmental risk factors compared to those who did not use cannabis (Loberg and Hugdahl, 2009; Schnell et al., 2009; Leeson et al., 2012). Another explanation is that early cannabis use may induce psychosis onset in less cognitively vulnerable individuals, i.e., those with better cognitive capacities, thereby facilitating the onset of psychosis that may otherwise not have occurred (Yucel et al., 2012). A related suggestion is that the better cognition in patients who use cannabis may have facilitated their recreational drug use like in typical adolescents (Ferraro et al., 2013), or that superior social skills enable cannabis-using patients to acquire and sustain a drug habit, which is reflected in their cognition (Solowij and Michie, 2007; Potvin et al., 2008).

When assessing the relationship between cannabis and IQ, it is important to control for the effects of the consumption of other substances. Tobacco and alcohol are the most frequently used substances among people with schizophrenia and in CHR than in the general population (de Leon and Diaz, 2005; Addington et al., 2014; Buchy et al., 2015a) and have been associated with neurocognitive function in schizophrenia (Fowler et al., 1998; Allen et al., 1999; Cantor-Graae et al., 2001; Manning et al., 2009; Yip et al., 2009; Wing et al., 2011; Morisano et al., 2013). Stimulant use also has a deleterious effect on cognitive functions in people diagnosed with a psychotic disorder (Serper et al., 2000a, 2000b; Smelson et al., 2003; Bahorik et al., 2014; van der Meer et al., 2014), and other studies have reported elevated neurocognition in people with schizophrenia currently using cocaine (Bahorik et al., 2014; Benaiges et al., 2013). Therefore, these variables must be taken into account when interpreting results of the relationship between cannabis use and IQ across the schizophrenia spectrum.

The goal of the present study was to assess the relationship between cannabis use patterns and IQ in CHR youth, while controlling for any use of other substances known to impact cognition such as tobacco, alcohol and stimulants, as well as antipsychotic medications. This cohort offers a unique opportunity to examine these associations prior to the onset of psychosis, in people with a greater probability of developing a psychotic disorder relative to the general population, but who do not have potential confounds seen in patient studies such as lengthy antipsychotic treatment. Based on the literature in schizophrenia, we hypothesized that: 1) CHR youth using cannabis will have a higher IQ compared to those who do not; 2) CHR youth with a lifetime exposure to cannabis will have a higher IQ compared to never-users; and 3) CHR low-frequency cannabis users will have a higher IQ than CHR high-frequency users. Additionally, we conducted exploratory analyses of IQ in relation to age at onset of cannabis use in CHR youth, and in CHR separated dichotomously by early vs. late age at onset of cannabis. We also conducted an exploratory analysis of IQ in CHR converters vs. non-converters separated by baseline cannabis use (Y/N).

2. Methods

2.1. Participants

Participants were recruited for the second phase of the multi-site North American Prodrome Longitudinal Study (NAPLS-2) (Addington et al., 2012). The final NAPLS-2 sample consists of 764 CHR participants and 280 healthy controls (HC). The present paper reports on the 678 CHR and 263 HC participants in NAPLS 2 who provided baseline IQ data and completed an assessment on cannabis use. All CHR participants were required to meet the Criteria of Prodromal Syndromes (COPS) using the Structured Interview for Prodromal-Risk Syndromes (SIPS) (McGlashan et al., 2010). The age range for NAPLS-2 was 12–35.

Participants were excluded if they met criteria for any current or lifetime axis I psychotic disorder, IQ < 70, past or current history of a central nervous system disorder or DSM-IV criteria for a current substance dependence disorder. HC participants were also excluded if they had a first-degree relative with a current or past psychotic disorder. HC and CHR participants were not matched for IQ; however, we made every attempt to match groups on age, sex and parental socioeconomic status. A more detailed description of ascertainment, inclusion and exclusion criteria, and participant details is provided elsewhere (Addington et al., 2012).

2.2. Measures

The SIPS and the Scale of Prodromal Symptoms (SOPS) (McGlashan et al., 2010) were used to assess criteria for a prodromal syndrome and severity of attenuated positive symptoms.

Diagnosis of conversion to psychosis was made with the SCID (First et al., 1998). Conversion criteria is that at least one of the five SOPS positive symptoms reached a psychotic level of intensity (rated 6) for a frequency of ≥ 1 h per day for 4 days per week during the past month or that symptoms seriously impacted functioning (e.g., severely disorganized or dangerous to self or others).

Alcohol and drug use for cannabis, cocaine and amphetamine severity over the last month was rated using the Alcohol and Drug Use Scale (AUS/DUS) (Drake et al., 1996) as 1=abstinent, 2=use without impairment, 3=abuse, 4=dependence. Frequency of use was rated as 0=no use, 1=once or twice per month, 2=3–4 times per month, 3=1–2 times per week, 4=3–4 times per week, or 5=almost daily. Frequency of tobacco use was rated differently as 0=no use, 1=occasionally, 2=less than 10 per day, 3=11–25 per day, 4=more than 25 per day. Based on commonly used measures and interview questions in the literature (Arseneault et al., 2002; Caspi et al., 2005; Henquet et al., 2005), we also enquired whether they had ever used cannabis during their lifetime (i.e. “Have you ever smoked/used cannabis?”) and the age at first use.

IQ was estimated with the Vocabulary and Block Design subtests of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

2.3. Cannabis groups

First, we separated CHR participants into three groups of users: early-onset (< age 15), late-onset (≥ age 15), and cannabis naïve.

Next, CHR individuals were grouped according to baseline cannabis use frequency and compared on IQ: Abstinent, low-frequency (< 5 times per month), moderate-frequency (< 5 times per week), and high-frequency users (Daily).

Lastly, we separated CHR youth into four sub-groups according to baseline cannabis use and subsequent conversion vs. non-conversion to psychosis: CHR who converted and were using cannabis (Converter+Cannabis), CHR who converted and were abstinent (Converter−Cannabis), CHR who did not convert and were using cannabis (NonConverter+Cannabis), and CHR non-converters abstinent from cannabis (NonConverter−Cannabis).

2.4. Procedures

All eight NAPLS sites (Emory University, Harvard University/Beth Israel Deaconess Medical Center, University of Calgary, University of California at Los Angeles, University of California at San Diego, University of North Carolina at Chapel Hill, Yale University, and Zucker Hillside Hospital) recruited CHR and HC participants. Raters were experienced research clinicians who demonstrated adequate reliability at routine reliability checks. Post-training agreement on the critical threshold for determining initial eligibility, subsequent conversion status and prodromal diagnoses based on the SIPS was excellent (kappa=.90). All testers across sites received training on IQ measures at the beginning of the study under the supervision of LJS and WS and ongoing within site and across site supervision was carried out at least a few times every month (Meyer et al., 2014). The Principal Investigator or clinical psychiatrist or psychologist at each site conducted a comprehensive clinical assessment to determine if entry criteria were met (Addington et al., 2012). Clinical assessments that included the AUS/DUS were conducted at baseline. The study protocols and informed consents were reviewed and approved

by the ethical review boards of all eight NAPLS study sites. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.5. Statistical analysis

Chi-square or Fisher's Exact analyses for categorical variables and *t*-tests for continuous variables were used to compare CHR and HC groups on demographic variables and substance use. *t*-Tests were used to compare participants using cannabis at baseline vs. those who were abstinent on IQ. Spearman's correlations were used to evaluate associations of age at onset of cannabis use with IQ scores. ANCOVAs were then used to determine the relationship between IQ and cannabis use patterns while controlling statistically for the effects of confounding variables (demographics, alcohol, tobacco, cocaine and amphetamine use). Univariate ANOVAs were used to compare IQ in the following groups: 1) early-onset, late-onset, and naïve, and 2) CHR abstinent, low-frequency, moderate-frequency, and high-frequency. Similarly, ANCOVAs were then used to determine the relationship between IQ and cannabis use groups while controlling statistically for the effects of confounding variables (see above). Tukey's post-hoc tests were used to compare groups where appropriate. The *p*-value was set to 0.05/6=0.008 to correct for the number of comparisons with IQ. Statistical analyses were performed using SPSS 21.0.

3. Results

3.1. Demographics, cannabis use patterns and IQ

In the entire sample, males and females did not significantly differ on IQ, $t=0.24$, $p=0.81$. Age and years of education showed small but significant positive correlations with IQ scores, $r=0.11$, $p=0.001$; $r=0.18$, $p<0.001$, respectively. Alcohol use was also significantly correlated with IQ, $r=0.20$, $p<0.001$. Tobacco, cocaine and amphetamine use did not significantly correlate with IQ, $r=0.007$, $p=0.83$; $r=-0.02$, $p=0.38$; $r=0.02$, $p=0.50$, respectively. In CHR, baseline IQ did not differ in those taking antipsychotics from those not taking antipsychotics, $t=0.92$, $p=0.36$. Therefore, years of education and alcohol use were entered as covariates in all analyses.

As summarized in Table 1, HC participants were significantly older and had greater years of education than CHR participants. These groups did not differ on gender or race.

Table 2 displays cannabis use patterns of the CHR and HC groups. These groups did not differ on baseline cannabis use frequency, lifetime cannabis exposure, number of users at baseline, or age at onset of cannabis use. However, CHR participants had significantly higher baseline cannabis use severity.

HC had significantly higher IQ than CHR participants, $t=4.62$, $p<0.001$; $M=109.5$, SD=14.0 and $M=104.5$, SD=15.4, respectively.

Table 1
Demographic and clinical characteristics of the clinical high risk and healthy control groups.

	CHR ***n*=678** ***n* (%)**	**HC** ***n*=263** ***n* (%)**	χ^2	***p*-value**
Sex				
Male	390 (58)	136 (52)	2.60	0.11
Female	288 (42)	127 (48)		
Race[a]				
First Nations	13 (1.9)	5 (1.9)	3.56	0.94
Asian	52 (7.7)	24 (9.2)		
Black	103 (15.2)	48 (18.3)		
Latin America/Middle East/ White	427 (62.9)	156 (59.2)		
Native Hawaiian/Pacific Islander	3 (0.4)	1 (0.4)		
Inter-racial	78 (11.5)	29 (11.0)		
	Mean (SD)	**Mean (SD)**	***t***	***p*-value**
Age (years)	18.5 (4.3) Range: 12–34	19.7 (4.6) Range: 12–35	3.78	<0.001
Education (years)	11.3 (2.8)	12.7 (3.6)	6.34	<0.001

Note. CHR, Clinical High Risk; HC, Healthy Controls; SD, Standard Deviation.
[a] Racial information was missing for two participants.

3.2. Relationship between IQ and cannabis use patterns when stratifying by CHR/controls

IQ scores in CHR and HC participants stratified by cannabis use are reported in Table 3.

3.2.1. Baseline use

To test hypothesis 1, we evaluated IQ in CHR and HC cannabis users vs. non-users at baseline. In CHR participants, IQ was significantly higher among those who were using cannabis (age range 12–35) compared with those who were not (age range 12–31), $t=2.82$, $p=0.005$, Cohen's $d=0.22$. In contrast, in HC participants, there was no statistically significant difference in IQ scores between those who were (age range 12–34) or were not (age range 12–34) using cannabis, $t=0.49$, $p=0.63$. An ANCOVA adjusting for years of education and alcohol use in the CHR group indicated that the group difference in IQ was no longer significant, $F(1,668)=0.53$, $p=0.47$. The result in the HC group remained non-significant when adjusting for the same covariates with ANCOVA, $F(1,244)=0.49$, $p=0.48$.

3.2.2. Lifetime exposure

To test hypothesis 2, we evaluated IQ in CHR and HC with a positive vs. negative lifetime exposure to cannabis. CHR participants who reported a positive lifetime exposure (age range 12–35) had a higher IQ than those who had never used cannabis (age range 12–33), $t=3.38$, $p=0.001$, Cohen's $d=0.26$. By contrast, HC participants with (age range 12–34) and without a lifetime exposure to cannabis (age range 12–34) did not significantly differ on IQ scores, $t=0.60$, $p=0.55$. An ANCOVA adjusting for years of education and alcohol use in the CHR group indicated that this result was no longer significant, $F(1,668)=0.01$, $p=0.93$. The result in the HC group did not change when adjusting for the covariates with ANCOVA, $F(1,258)=2.00$, $p=0.16$.

3.2.3. Relationship between IQ and cannabis use frequency

To test hypothesis 3, we evaluated IQ in CHR participants categorized according to baseline cannabis use frequency. Nineteen (3.0%) admitted to high-frequency use, 46 (4.9%) to moderate-frequency use, 75 (12.1%) to low-frequency use and 537 (78.0%) were abstinent (data were missing for one participant; age ranges: 13–29; 13–30; 13–31; 12–35, respectively). Demographic and clinical characteristics as well as IQ scores for these groups are presented in Supplemental Table 1. IQ scores are presented in Table 3. These groups significantly differed in age, education, and SOPS total attenuated positive symptoms, as well as cannabis, alcohol, tobacco, cocaine, and amphetamine use. Thus, these eight variables were entered as covariates using ANCOVA.

The group effect in the ANCOVA was non-significant, $F(3,641)=0.61$, $p=0.61$, indicating that CHR participants classified according to cannabis use frequency did not differ on IQ.

3.3. Relationship between age at cannabis use onset and IQ in CHR

To test exploratory hypothesis 1, we first correlated IQ with age at onset of cannabis use in CHR participants. Age at onset of cannabis use was significantly and positively correlated with IQ

Table 2
Rates and patterns of cannabis and other drug use over lifetime in clinical high risk and healthy control participants.

	CHR $n=678$ Mean (SD)	HC $n=263$ Mean (SD)	Statistic t	p-value
Cannabis				
Number of times used in lifetime[a]	63.7 (109.5)	41.9 (89.4)	2.88	0.004
Age first tried[b]	15.7 (2.9)	16.2 (2.5)	1.62	0.11
	***n* (%)**	***n* (%)**	χ^2	***p*-value**
Current user: Yes	149 (22.0)	43 (16.3)	3.32	0.07
Lifetime exposure: Yes	351 (51.8)	128 (48.7)	0.73	0.39
Use severity[c]				
Abstinent	538 (79.4)	220 (83.7)	6.71	0.08
Use without impairment	116 (17.1)	41 (15.6)		
Abuse	22 (3.2)	2 (0.8)		
Dependence	2 (0.3)	0 (0.0)		
Use frequency for current users[c]				
1–2 × per month	55 (41.6)	18 (6.8)	4.66	0.46
3–4 × per month	20 (13.4)	6 (2.3)		
1–2 × per week	26 (18.1)	6 (2.3)		
3–4 × per week	20 (13.4)	9 (3.4)		
Every day	19 (12.8)	4 (1.5)		
Missing	1 (0.6)	0 (0.0)		
Tobacco			**Fisher's exact *p*-value**	
Use severity[c]				
Abstinent	532 (78.5)	227 (86.3)	0.04	
Use without impairment	136 (20.1)	32 (12.2)		
Abuse	5 (0.7)	0 (0.0)		
Dependence	5 (0.7)	2 (0.8)		
Missing	0 (0.0)	2 (0.8)		
Other drug use				
Alcohol				
Abstinent	412 (60.8)	133 (50.6)	0.01	
Use without impairment	249 (36.7)	126 (47.9)		
Abuse	13 (1.9)	3 (1.1)		
Dependence	4 (0.6)	0 (0.0)		
Cocaine				
Abstinent	667 (99.3)	262 (99.6)	0.47	
Use without impairment	1 (0.1)	1 (0.4)		
Abuse	0 (0.0)	0 (0.0)		
Dependence	0 (0.0)	0 (0.0)		
Amphetamine				
Abstinent	667 (99.9)	261 (99.2)	0.19	
Use without impairment	1 (0.1)	2 (0.8)		
Abuse	0 (0.0)	0 (0.0)		
Dependence	0 (0.0)	0 (0.0)		

Abbreviations: CHR=Clinical High Risk, HC=Healthy Control, SD=Standard Deviation

[a] Excludes never-users.
[b] Excludes people who had never used cannabis.
[c] Measured with the Alcohol and Drug Use Scale.

scores, $r=0.26$, $p<0.001$ (see Fig. 1). The correlation between age at onset and IQ scores was non-significant in the HC group, $r=0.16$, $p=0.08$. In CHR, when controlling for years of education and alcohol use with partial correlation, the result remained significant, $r=0.16$, $p=0.004$. Adding total number of usages of cannabis across the lifetime as a covariate using partial correlation did not change results, $r=0.16$, $p=0.003$. In HC participants, adding the same covariates using partial correlation did not change the results, $r=0.12$, $p=0.18$.

3.4. Relationship between IQ and early age of onset of cannabis use

To test exploratory hypothesis 2, we evaluated IQ in CHR participants sub-grouped by age at onset of cannabis use. One-hundred twenty-two (18.0%) CHR participants had an early-onset, 227 (33.5%) had a late-onset, and 327 (48.2%) were cannabis naïve (data were missing for two participants; age ranges: 12–31; 12–33; 12–35, respectively). Demographic and clinical information for these three groups are presented in Supplemental Table 2. These groups significantly differed on age, education, SOPS total positive symptoms, as well as cannabis, alcohol, tobacco and cocaine use. Thus, these six variables were entered as covariates using ANCOVA.

When comparing these three CHR sub-groups on IQ, the ANCOVA indicated a significant main effect of group, $F(3,641)=6.13$, $p<0.001$, Partial $Eta^2=0.02$. Tukey's post-hoc tests indicated that the late-onset group had significantly higher IQ than the early-onset ($p<0.001$) and naïve CHR groups ($p=0.002$).

Table 3
IQ scores of CHR and healthy control participants stratified by cannabis use patterns.

	IQ score	
	CHR $n=678$ Mean (SD)	HC $n=263$ Mean (SD)
Currently using		
Yes	107.8 (14.9)	108.4 (15.0)
No	103.7 (15.4)	109.6 (13.8)
Lifetime exposure		
Yes	106.5 (14.7)	108.1 (14.1)
No	102.5 (15.9)	109.9 (13.9)
Age first tried		
Naïve ($n=327$)	102.5 (15.9)	
Early-onset ($n=122$)	102.0 (14.2)	–
Late-onset ($n=227$)	108.9 (14.4)	
Frequency		
Abstinent ($n=529$)	103.7 (15.5)	
Low-frequency ($n=82$)	108.6 (14.9)	–
Moderate-frequency ($n=27$)	106.9 (15.1)	
High-frequency ($n=20$)	109.3 (13.8)	

Abbreviations: CHR=Clinical High Risk, HC=Healthy Control, SD=Standard Deviation

3.5. IQ in CHR who converted to psychosis vs. CHR who did not convert to psychosis separated by baseline cannabis use vs. no use

To test exploratory hypothesis 3, we evaluated IQ in CHR participants categorized by baseline cannabis use vs. no use and subsequent conversion vs. non-conversion to psychosis. Using this categorization, 23 were in the Converter+Cannabis group, 61 in the Converter−Cannabis group, 118 in the Non-converter+Cannabis group and 476 in the Non-converter−Cannabis

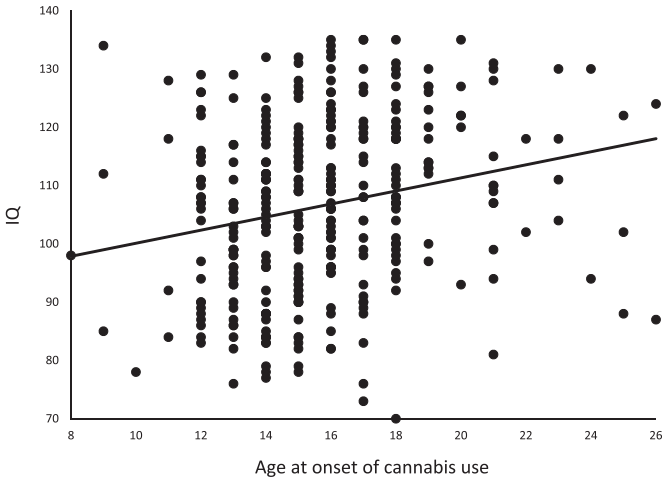

Fig. 1. Correlation between age at onset of cannabis use and IQ in CHR, $r=0.26$, $p<0.001$.

group; age ranges: 13–25; 12–28; 13–31; 12–35, respectively. Demographic and clinical information for these four sub-groups are presented in Supplemental Table 3. These sub-groups significantly differed on age, education, and alcohol and tobacco use. Thus, these four variables were entered as covariates using ANCOVA.

When comparing these four CHR groups on IQ, the ANCOVA indicated a significant main effect of Group, $F(3,661)=2.61$, $p=0.05$. As this effect was at trend level after correction for multiple comparisons, we conducted post-hoc tests to reveal potential group differences. Tukey's post-hoc tests indicated that the Non-converter+Cannabis group had significantly higher IQ than the Non-converter−Cannabis ($p=0.04$) and Converter+Cannabis group ($p=0.01$).

4. Discussion

The aim of the current work was to evaluate IQ in relation to patterns of cannabis use in a large CHR sample while controlling statistically for confounding demographic variables and use of other substances that are known to alter cognition. Results indicated that although both CHR participants with a positive lifetime exposure to cannabis use and CHR cannabis users at baseline showed higher IQ than CHR participants who were abstinent, these effects were confounded by age and other substance use. Thus, hypotheses 1 and 2 were not supported. Hypothesis 3 also received little support as CHR participants classified according to cannabis use frequency did not differ on IQ. On the other hand, our exploratory analysis indicated that in CHR participants, age at onset of cannabis use was significantly and positively correlated with IQ, and CHR participants with early-onset cannabis use (i.e., before age 15) and cannabis naïve CHR participants showed significantly lower IQ than CHR late-onset users (at or after age 15). Both effects survived when removing variance due to age and use of other substances, suggesting age at first use of cannabis may be a more important factor for IQ than use severity/frequency or lifetime exposure in people who are at CHR of psychosis.

CHR and HC participants with a positive lifetime exposure to cannabis use were indistinguishable on IQ from those who had never used cannabis. Our analysis of baseline users vs. non-users also suggested no differences in IQ in either CHR or HC groups. It should be noted that the positive lifetime exposure variable includes people who have used only once through people who use daily, thereby creating a heterogeneous group whose data are unlikely to yield meaningful information on which aspects of cannabis use relate to IQ. Yucel et al. (2012) also did not observe differences in IQ in their first-episode psychosis patients with a positive lifetime exposure to cannabis compared to never-users. However, two recent studies in first-episode psychosis reported higher IQ in patients with a positive lifetime exposure compared to never-exposed patients (Leeson et al., 2012; Ferraro et al., 2013), and retrospective data from a large cohort of Swedish conscripts have suggested that lifetime cannabis exposure and low IQ may have an additive relationship on risk for developing psychosis (Zammit et al., 2010). That CHR cannabis users at baseline did not differ from CHR non-users is inconsistent with meta-analytic data in schizophrenia suggesting superior cognitive functioning in cannabis-using patients compared to non-using patients (Rabin et al., 2011). Our CHR sample had very few observations for "abuse" ($n=22$) or "dependence" ($n=2$), and analyses of samples with higher proportions of CHR youth with higher use severities may help clarify whether use severity is associated with IQ in this population. In light of our result, hypotheses that patients with schizophrenia who use cannabis are less neurodevelopmentally impaired than patients who did not use cannabis (Loberg and Hugdahl, 2009; Schnell et al., 2009; Leeson et al., 2012) may not extend to the CHR phenotype.

Categorizing CHR participants according to patterns of cannabis use frequency yielded no indication that low use frequencies were a differentiating factor for IQ in our sample. Although no studies have examined such relations in CHR individuals, one study in schizophrenia has reported higher premorbid IQ in low- compared to high-frequency users (Leeson et al., 2012), although another study failed to observe this relationship (Yucel et al., 2012). Our CHR sample had very few observations for moderate- and high-frequency users ($n=27$ and $n=22$, respectfully), and samples with higher representation in these categories may clarify whether an association between use frequency and IQ is seen in CHR youth. Our data do not provide support for the hypothesis that the neuroprotective properties of cannabis use accounts for observed relations between low frequency cannabis use and a higher IQ in schizophrenia (Jockers-Scherubl et al., 2007).

Perhaps the most novel result from our analyses is the significant correlation that emerged between IQ and age at onset of cannabis use in our CHR sample, although it should be noted that the effect size of the correlation coefficient was small ($r=0.26$). This result was not observed in HC participants, suggesting a specific effect that is unique to the CHR status. A younger age at onset is now emerging as an important environmental risk factor in CHR youth, with findings suggesting that younger age at first usage confers greater risk for conversion to psychosis (Valmaggia et al., 2014), an earlier age at onset of prodromal and psychotic symptoms (Leeson et al., 2012), as well as altered brain activation patterns (Buchy et al., 2015b) and white matter microstructure (Dekker et al., 2010). That age at onset of cannabis use had a positive and linear association with IQ suggests that an older age at first use may be a protective factor for a higher IQ in CHR youth. Alternatively, a higher IQ may lead CHR individuals to delay the onset of their cannabis use during adolescence. Interestingly, this effect extended to CHR youth dichotomized into early- vs. late-onset groups, suggesting that first use before age 15 shares a particularly negative relationship with IQ in our sample. It should be noted that Yucel et al. (2012) did not observe differences in IQ in psychosis patients with an early vs. late age at onset of cannabis use; however, these authors defined early age at onset of cannabis use as age 17, which may account for discrepancy in findings. In concert, the results from the current study suggest that IQ is associated with the age of exposure to cannabis in a linear fashion and there may be a specific interaction with IQ when exposure occurs during a sensitive period in development. This result also has implications for current theories of cannabis use and IQ in schizophrenia. For instance, these older individuals may form a subgroup of higher intellectually functioning individuals who may also be less neurodevelopmentally impaired (Loberg and Hugdahl, 2009; Schnell et al., 2009; Leeson et al., 2012) and/or have higher social functioning than CHR individuals with an earlier age at onset (Ferraro et al., 2013).

Our analysis of CHR converters vs. non-converters sub-grouped by baseline cannabis use vs. no-use revealed some interesting findings. First, non-converters using cannabis showed higher IQ than non-converters abstinent from cannabis. Other studies have shown higher IQ in cannabis using individuals with psychosis (Yucel et al., 2012), and the current result suggests that this pattern may also be present in people at CHR of developing the disorder. Thus our result provides support for accounts holding that those using cannabis are less neurodevelopmentally impaired than those who are not (Loberg and Hugdahl, 2009; Schnell et al., 2009; Leeson et al., 2012), and that cannabis users have less premorbid cognitive impairment than those who are abstinent (Joyal et al., 2003; Rodriguez-Sanchez et al., 2010; Stirling et al., 2005). Second, non-converters using cannabis at baseline showed higher IQ than

converters using cannabis at baseline. This finding may suggest that in people at clinical risk for psychosis, a lower IQ may be a risk factor for conversion, or higher IQ may be a protective factor against conversion (Woodberry et al., 2010). Converters using cannabis did not differ from abstinent converters. This negative result is inconsistent with other findings in first-episode psychosis (Leeson et al., 2012; Ferraro et al., 2013), and the small number of people in these groups may have rendered this analysis underpowered to detect a significant effect. Interestingly, there is very recent evidence suggesting that among people with a psychotic disorder, those who use tobacco daily developed a psychosis at an earlier age compared to those who were abstinent from tobacco (Gurillo et al., 2015). Future research may consider evaluating the relationship between tobacco and/or cannabis use, IQ, and age at onset of psychosis in samples of people at clinical high risk of psychosis.

Limitations include the self-report ascertainment of cannabis use, which may be less reliable than collection of biologically based specimens such as urine toxicology data or other biochemical verification of cannabis use. A recent study evaluating concordance between self-report and urine screening for cannabis in youth at risk for psychosis has shown poor consistency between urine results and self-reported use, such that some individuals reported cannabis usage but urine screens are negative, whereas others did not report cannabis use but the urine screen detected tetrahydrocannabinol. Further, details on cannabis dosage were not collected and therefore their potential impact on IQ cannot be determined. The current CHR sample is more representative of individuals with recreational rather than heavy, problematic cannabis use, and this should be considered when relating the current findings to previously published studies in schizophrenia. Our analysis of positive lifetime exposure included people who have used only once in their lifetime through people who use daily, and more stringent inclusion criteria regarding prior cannabis use may provide a more homogeneous group to evaluate relationships between cannabis use and IQ. Nevertheless, the results provide partial support for findings in schizophrenia, and extend these results by establishing a link between an older age at onset of cannabis use and higher IQ in CHR. Interestingly, many of the results reported in the current study were non-significant when accounting for alcohol use at baseline. There is now data from a large sample of youth at CHR for psychosis indicating that accounting for alcohol use weakened an observed relationship between cannabis abuse or cannabis dependence and conversion to psychosis (Auther et al., 2015). These findings, along with the current results, highlight the importance of controlling for confounding variables. Given the high prevalence of alcohol use in CHR samples (Addington et al., 2014), cannabis use is likely confounded by the use of this substance much of the time (Auther et al., 2015). Future research in CHR samples should examine individuals' long-term cannabis use patterns and its covariation with IQ over time, while considering the impact of confounding variables such as alcohol and other drug use. Furthermore, in light of the current results, future works may include age at onset of cannabis use, baseline cannabis use and IQ in prediction models of conversion to psychosis.

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Conflict of Interest

All authors declare no conflict of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2015.11.033.

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