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Association of early onset of cannabis, cigarette, other drug use and schizophrenia or psychosis

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To the Editors,

Schizophrenia affects 0.25-0.64% of the United States population (National Institute of Mental Health, 2018). While national prevalence remains low, the financial burden of schizophrenia and other psychosis is disproportionately high due to the many direct and indirect costs of the illness including frequent hospitalizations, need for psychosocial services, and loss of productivity (National Institute of Mental Health, 2018). A constellation of complex factors have been associated with the development of schizophrenia and related psychosis including abnormal brain structure, altered neurotransmitter systems, and genetic and environmental factors. Both cigarette and cannabis use in early adolescence have been correlated with development of schizophrenia/psychosis (Gage et al., 2014; Jones et al., 2017). However, important confounding factors have created significant difficulty in assessing the causal relationship between substance use and schizophrenia/psychosis.

Two large community-based studies in the United States (US) and United Kingdom showed that dual cannabis and cigarette use was associated with psychosis (Gage et al., 2014; Jones et al., 2017). However, these data were limited by small samples. To address this limitation, Davis et al. (2013) used data derived from the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-II) and found that cannabis use was related to schizophrenia/psychosis in a dose dependent manner, however the authors did not adjust for possible covariates including cigarette, alcohol, and polysubstance use. Adjusting for concomitant substance use is important as many early adolescent cannabis users also use other substances (Moss et al., 2014), and a majority (70-85%) of individuals with schizophrenia smoke cigarettes (Ziedonis et al., 2008). Thus, we examined the most recent

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Contributions:

Drs. Ryan, Boyd, McCabe and Stoddard designed the study and conducted the literature searches. Drs. Ryan and Veliz conducted the statistical analyses and data interpretation. Dr. Ryan wrote the first draft of the manuscript, and all authors contributed to and have approved the final manuscript.

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NESARC-III data to determine whether there was a relationship between substance use and schizophrenia/psychosis when adjusting for important covariates.

Data come from the NESARC-III, a nationally representative survey of the civilian noninstitutionalized population of U.S. adults (>18 years). The final sample (N=36,309) reflected an overall response rate of 60.1%. The sample design, response rates, and weighting procedures are described elsewhere (Grant et al., 2015). The independent variable was lifetime diagnosis of schizophrenia or other psychosis which was determined by asking the respondent: “Did a doctor or other health professional ever diagnose you with schizophrenia or a psychotic illness or episode?” [Yes/No]. This question has been validated, and is consistent with prevalence rates in North America (Supina and Patten, 2006). To determine new onset of schizophrenia/psychosis, the analytical sample was restricted to 18-34 year olds (N=11,755), with 264 respondents answering ‘yes’ to having a lifetime diagnosis of schizophrenia/psychosis. The Alcohol Use Disorder and Associated Interview Schedule (AUDADIS-5) was used to assess dependent variables including substance use, risk factors, and mental and physical disabilities. Information on the validity and reliability of the AUDADIS-5 have been published elsewhere (Grant et al., 2015). The AUDADIS-5 includes questions regarding drug specific use for cannabis, cigarettes, alcohol and nine other classes of drugs (See table 1, and supplementary 2). Other complex factors have been associated with increased likelihood of schizophrenia/psychosis including sexual orientation (Bolton and Sareen, 2011), race (Olbert et al., 2018), history of trauma (Lysaker et al., 2010), and family history of substance use (Jones et al., 2017). We therefore included these covariates in adjusted models. (See table 1, and supplementary table 2).

Results of our analysis showed that individuals with schizophrenia/psychosis were significantly more likely to have a history of trauma (66% vs. 41%, $p<0.001$), family history of drug related problems (53% vs 42%, $p=0.007$), and identify as bisexual (14% vs 2%, $p<0.001$). Individuals with schizophrenia/psychosis also were significantly more likely to have used cannabis (38% vs 22%, $p=0.001$), cigarettes (36% vs 22%, $p<0.001$) and alcohol (37% vs 28%, $p=0.023$), and other drugs before age 16 years (21% vs 8%, $p<0.001$). Early adolescent cannabis use was associated with a 2-fold increase in schizophrenia/psychosis (OR 2.02, CI 1.35-3.01, $p=0.001$). However, when adjusting for other variables (sex, race, education, income, history of trauma, sexual orientation, and family history of substance problems), the association was no longer significant (aOR 1.47, CI .99-2.18, $p=0.054$). Cigarette use in both early and late adolescence was associated with a 2-fold increase in schizophrenia/psychosis, (early use OR 2.44, CI 1.75-3.4, $p<0.001$; late use OR 2.12, CI 1.37-3.26, $p=0.001$). When adjusting for covariates the association remained significant (early use aOR 1.91, CI 1.32-2.71, $p<0.001$; late use aOR 1.83, CI 1.16-2.88, $p=0.01$). Alcohol use before age 16 was significantly associated with schizophrenia/psychosis (OR 2.15, CI 1.11-4.16, $p=0.023$), later use was not. Other drug use was significantly correlated with schizophrenia/psychosis in all models. In unadjusted models, other drug use before 16 years old was associated with a 3-fold increase in schizophrenia/psychosis (OR 3.08, CI 1.91-4.99, <0.001).

We found that a majority of individuals (78%) with schizophrenia/psychosis who reported using cigarettes before 16, also reported using marijuana, alcohol, and other drugs. In

analytic models that included concomitant use of cigarettes + cannabis (models 5,12), only cigarette use was significantly associated with schizophrenia/psychosis (aOR 1.75, CI 1.25-2.46, $p=0.001$ for cigarettes; OR 1.16, CI 0.78-1.74, $p=0.447$ for cannabis). In models of early cannabis + cigarette + alcohol use (models 6, 13) only cigarette use was associated with schizophrenia/psychosis (aOR 1.69, CI 1.21-2.36, $p=0.002$ for cigarettes; aOR 1.12, CI 0.76-1.63, $p=0.565$ for cannabis; aOR 1.27, CI 0.66-2.45, $p=0.468$ for alcohol). (See table 1)

In conclusion, we found little support for an association between cannabis use and the development of schizophrenia/psychosis among adults aged 18-34 after adjusting for covariates such as history of trauma, sexual orientation, other substance use and family substance-related problems. We observed that cigarette use in early and late adolescence was associated with higher odds of reporting a lifetime diagnosis of schizophrenia/psychosis, and other drug use was consistently associated with schizophrenia/psychosis. This study highlights the importance of considering confounding factors such as polysubstance use when describing the relationship between cannabis use in early adolescence and schizophrenia or psychosis, and the need for more prospective research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association between Schizophrenia/Psychosis and Substance Use in Early Adolescence Sub-sample included 18-34 years olds, who ever had diagnosis of schizophrenia/psychosis

	OR (95% CI)	P value	aOR (95% CI) *	P value
<u>Cannabis</u>	<u>Model 1</u>		<u>Model 8</u>	
Never or unknown	reference		reference	
Early cannabis use (<16 years old ^a)	2.02 (1.35, 3.01)	0.001	1.47 (.99,2.18)	0.054
Late cannabis use (>16 years old)	0.85 (0.51,1.41)	0.521	0.71 (0.41, 1.21)	0.204
<u>Cigarette</u>	<u>Model 2</u>		<u>Model 9</u>	
Never or unknown	reference		reference	
Early cigarette use (<16 years old ^b)	2.44 (1.75,3.4)	<0.001	1.91 (1.34,2.71)	<0.001
Late cigarette use (>16 years old)	2.12 (1.37,3.26)	0.001	1.83 (1.16, 2.88)	0.010
<u>Alcohol</u>	<u>Model 3</u>		<u>Model 10</u>	
Never or unknown	reference		ref reference	
Early alcohol use (<16 years old ^c)	2.15(1.11,4.16)	0.023	1.66 (0.86, 3.2)	0.128
Late alcohol use (>16 years old)	1.39 (0.8,2.4)	0.239	1.25 (0.72,2.19)	0.423
<u>Polysubstance Use^d</u>	<u>Model 4</u>		<u>Model 11</u>	
Early drug use (<16 years old ^e)	3.08 (1.91,4.99)	<0.001	2.24 (1.34,3.72)	0.002
Late drug use (<16 years old)	1.8 (1.22,2.69)	0.003	1.45 (.96,2.19)	0.077
<u>Cannabis + Cigarettes^f</u>	<u>Model 5</u>		<u>Model 12</u>	
Early cannabis use (<16 years old)	1.43 (.93,2.18)	0.100	1.16 (0.78, 1.74)	0.447
Early cigarette use (<16 years old)	2.02 (1.44,2.83)	<0.001	1.75 (1.25, 2.46)	0.001
<u>Cannabis + Cigarettes +Alcohol^g</u>	<u>Model 6</u>		<u>Model 13</u>	
Early cannabis use (<16 years old)	1.35 (0.9,2.03)	0.144	1.12 (0.76, 1.63)	0.565
Early cigarette use (<16 years old)	1.94 (1.39, 2.7)	<0.001	1.69 (1.21,2.36)	0.002
Early alcohol use (<16 years old)	1.31 (0.67,2.54)	0.429	1.27 (0.66,2.45)	0.468
<u>Cannabis + Cigarettes + Alcohol + Drugs^h</u>	<u>Model 7</u>		<u>Model 14</u>	
Early cannabis use (<16 years old)	1.1 (0.72,1.69)	0.660	0.96 (0.64,1.42)	0.830
Early cigarette use (<16 years old)	1.79 (1.26,2.54)	0.001	1.6 (1.13,2.25)	0.008
Early alcohol use (<16 years old)	1.23 (0.63,2.41)	0.541	1.22 (0.63,2.38)	0.553
Early drug use (<16 years old)	2.15 (1.31, 3.54)	0.003	1.88 (1.13,3.11)	0.015

Abbreviations: 95% CI, 95% Confidence Interval; OR, odds ratio; aOR, adjusted odds ratio

* adjusted for age, sex, race, education level, income level, history of trauma, sexual orientation, and family history of alcohol-related problems and/or other drug-related problems (results for these covariates not shown).

^a How old were you when you FIRST used (name of drug category)? All responses >16 coded as 2, all responses <=16 coded as 1, unknown or never coded as 0.

^b About how old were you when you smoked your FIRST full cigarette? All responses >16 coded as 2, all responses <=16 coded as 1, unknown or never coded as 0.

^c About how old were you when you first started drinking, not counting small tastes or sips of alcohol? All responses >16 coded as 2, all responses <=16 coded as 1, unknown or never coded as 0.

^d Other drugs include sedatives or tranquilizers, painkillers, cocaine or crack, stimulants, club drugs, hallucinogens, inhalants/solvents, heroin, or other

^e How old were you when you FIRST used (name of drug category including: sedatives or tranquilizers, painkillers, cocaine or crack, stimulants, club drugs, hallucinogens, inhalants/Solvents, heroin, other). All responses for any drug category >16 coded 2, as all responses <=16 coded as 1, unknown or never coded as 0.

^f Adjusted for cannabis and cigarettes

^g adjusted for cannabis, cigarettes, and alcohol

^h adjusted for cannabis, cigarettes, and other drugs