

Heroin overdose death rates climbed after 2010.¹ We specified random-effects meta-analysis comparisons of 2 intervals and found that, from 2006 to 2010, risk of dependence was 23.7% (95% CI, 16.8%-30.6%) vs 41.7% (95% CI, 35.3%-48.0%) from 2011 to 2016. We then explored 2002 to 2010 and derived an estimate of 20.1% (95% CI, 15.5%-24.7%). We compared the estimate of 20.3% (95% CI, 14.6%-25.9%) in 2002 to 2009 with 39.9% (95% CI, 31.4%-48.5%) from 2010 to 2016.

Discussion | When observed within approximately 1 to 12 months after heroin onset, an estimated 23% to 38% of new heroin users have become dependent on heroin. Rank-order correlation and post hoc exploratory analyses prompt a hypothesis of recently increased odds of becoming dependent on heroin.

Seeking estimates for comparison, we found 3 published studies on how often heroin dependence was found among people who have used heroin at least once in their lifetime. The National Comorbidity Survey (1990-1992) estimate was 23% dependence rate (with a standard error [SE] of 5%); National Epidemiologic Survey on Alcohol and Related Conditions (2001-2002) estimate (SE) was 28% (4%); and National Epidemiologic Survey on Alcohol and Related Conditions-III (2012-2013) estimate (SE) was 25% (2%).^{4,6} These 3 values yield a random-effects meta-analysis summary of 26%, with a 95% CI of 22% to 29%, which clearly overlaps this study's overall finding of 23% to 38% of all participants becoming heroin dependent soon after first heroin use.

Limitations. In comparing this article with other surveys, differences in methods deserve consideration (eg, recall errors; cumulative odds of competing heroin dependence-associated risks, such as fatal overdose or incarceration; and left-truncation processes).^{5,6} In addition, estimates for 2002 through 2005 are from random-effects meta-analysis models and should be considered as post hoc exploratory data analyses completed after visual inspection of the year-specific estimates. Finally, all conclusions are subject to reevaluation when 2017 to 2018 NSDUH data files are released.

Conclusions | Irrespective of whether US heroin users now experience increased odds of becoming heroin-dependent, general principles indicate that primary prevention and early outreach initiatives are needed to control the spread of the nation's current heroin epidemic. We now lack evidence-based interventions for new heroin users before dependence develops and before medication-assisted treatment is indicated. Neglect of new users might foster incrementally greater challenges and costs in the expansions of heroin dependence treatment service responses to the current public health emergency.

Olga J. Santiago Rivera, PhD
Jennifer R. Havens, PhD
Maria A. Parker, PhD, MPH
James C. Anthony, PhD

Author Affiliations: Department of Epidemiology and Biostatistics, Michigan State University, East Lansing (Santiago Rivera, Parker, Anthony); Center on Drug and Alcohol Research, Department of Behavioral Science, University of

Kentucky College of Medicine, Lexington (Havens); Vermont Center on Behavior and Health, University of Vermont, Burlington (Parker).

Corresponding Author: James C. Anthony, PhD, Department of Epidemiology and Biostatistics, Michigan State University, B601 West Fee, East Lansing, MI 48824 (janthony@msu.edu).

Published Online: May 30, 2018. doi:10.1001/jamapsychiatry.2018.1214

Author Contributions: Dr Anthony had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Anthony, Santiago Rivera.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Santiago Rivera, Havens, Anthony.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Santiago Rivera, Parker, Anthony.

Obtained funding: Anthony.

Administrative, technical, or material support: Santiago Rivera, Anthony.

Study supervision: Anthony.

Conflict of Interest Disclosures: None reported.

Funding/Support: Support for this study from 2014 to 2016 came from the National Institute on Drug Abuse (grant T32DA021129) and National Institute on Drug Abuse Senior Scientist and Mentorship Award (grant K05DA015799 to Dr Anthony).

Role of the Funder/Sponsor: Neither the National Institute on Drug Abuse nor the universities with which the authors are affiliated had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is the sole responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse, the National Institutes of Health, or Michigan State University.

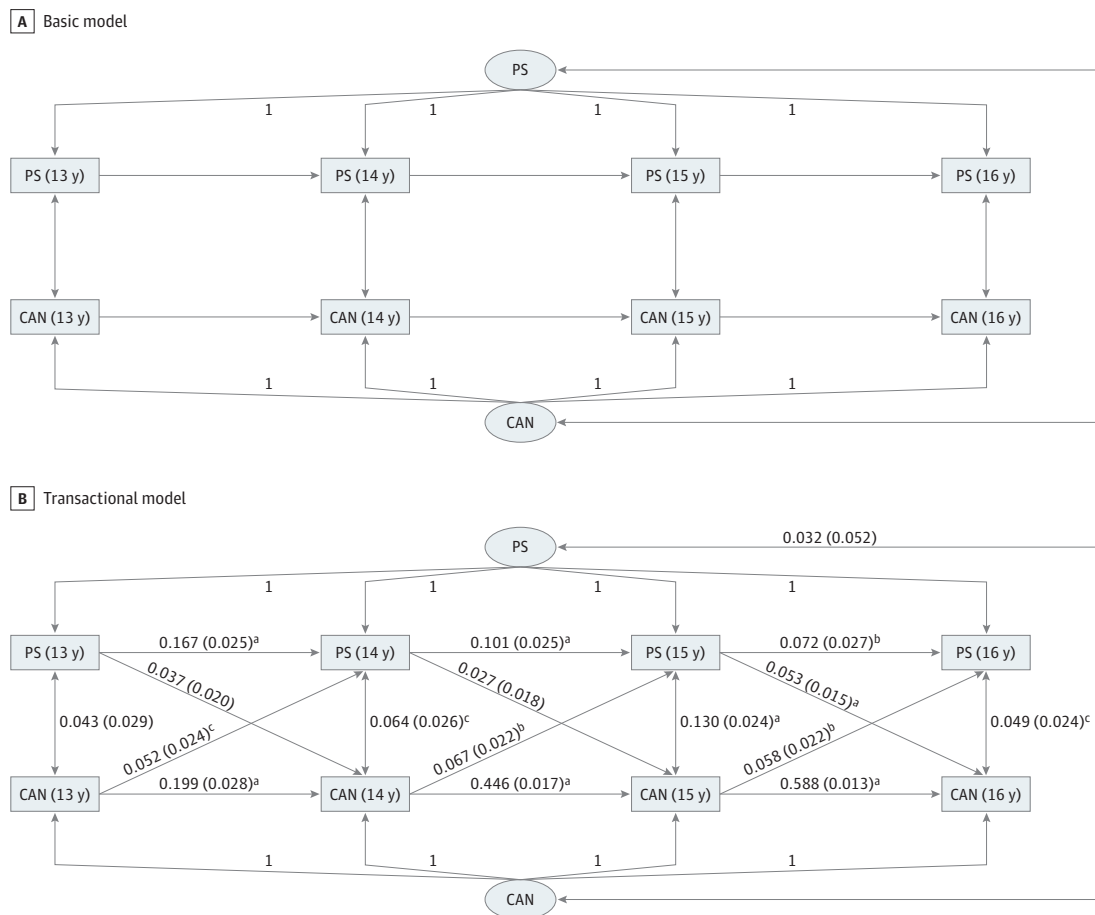
Additional Contributions: These data are from open access public use data files that can be downloaded as Public Use Files from the US Substance Abuse and Mental Health Data Archive web site (<https://pdas.samhsa.gov/#/>). The authors agree to provide Stata do-files to create the study variables by request to the senior author (Dr Anthony).

1. US Centers for Disease Control and Prevention; National Center on Health Statistics; National Vital Statistics System. Provisional counts of drug overdose deaths, as of 8/6/2017. https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf. Published 2017. Accessed April 9, 2018.
2. US Substance Abuse and Mental Health Services Administration; Center for Behavioral Health Statistics and Quality. Results from the 2016 National Survey on Drug Use and Health. https://www.samhsa.gov/sites/default/files/sites/default/files/2016_ffr_3_slideshow_v4.pdf. Published 2017. Accessed April 9, 2018.
3. US Substance Abuse and Mental Health Services Administration; Center for Behavioral Health Statistics and Quality. Accessing national and state data from the National Survey on Drug Use and Health. <https://archive.samhsa.gov/data/2k12/NSDUH116/NSDUHShortReport116AccessingData2012.htm>. Published August 3, 2012. Accessed April 9, 2018.
4. Martins SS, Sarvet A, Santaella-Tenorio J, Saha T, Grant BF, Hasin DS. Changes in US lifetime heroin use and heroin use disorder: prevalence from the 2001-2002 to 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*. 2017;74(5):445-455.
5. Parker MA, Anthony JC. Epidemiological evidence on extra-medical prescription pain relievers: transitions from newly incident use to dependence among 12-21 year olds in the United States using meta-analysis, 2002-13. *PeerJ*. 2015;3:e1340. doi:10.7717/peerj.1340
6. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: Basic findings from the National Comorbidity Survey. *Exp Clin Psychopharmacol*. 1994;2(3):244-268.

Association of Cannabis Use With Adolescent Psychotic Symptoms

Considering that jurisdictions are moving toward cannabis legalization and the anticipated changes to the Canadian policy planned for July 2018, there is a need to understand whether cannabis use has a causal role in the development of psychiatric diseases, such as psychosis. Prospective stud-

Figure. The Basic and Transactional Versions of the Random-Intercept Cross-Lagged Panel Model Between Cannabis Use (CAN) Frequency and Psychosis Symptoms (PS) During Adolescence (Age Range, 13-16 Years)



A, The basic model includes random intercepts (traitlike stability, also known as between-person differences), autoregressive paths (stability within a specific variable across time points), and cross-sectional correlations at each time point (within-time correlations across variables) but does not include cross-lagged paths (directional lagged associations between variables). B, The transactional model includes random intercepts, autoregressive paths, cross-sectional correlations, and cross-lagged paths. Only standardized parameter estimates are reported in the model. Both the basic model and the transactional model fitted the data well according to all 4 fit measures. For the basic model, $\chi^2_{15} = 48.22, P < .001$ (root-mean-square error of approximation [RMSEA], 0.02; Comparative Fit Index [CFI], 0.99; and standardized root-mean-square residual

[SRMR], 0.02); for the transactional model, $\chi^2_5 = 26.07, P = .002$ (RMSEA, 0.02; CFI, 1.00; and SRMR, 0.01). The χ^2 difference test favored the transactional model ($\Delta\chi^2_5 = 22.15, P = .001$). The first time point occurred at a mean age of 12.8 years. Twelve months separate each assessment. In total, 3226 (86.7%) and 3510 (94.4%) of participants had a minimum of 2 time points out of 4 on PS and CAN, respectively. The parenthetical after CAN and PS represents cannabis use frequency at the specified age.

^a $P < .001$.

^b $P < .01$.

^c $P < .05$.

ies report a temporal precedence of cannabis use before later onset of psychosis,¹ but the evidence is limited with respect to causality due to studies only assessing psychosis symptoms (PS) at a single follow-up and by relying on analytic models that might confound intra-individual processes with initial between-person differences. In the absence of an experimental design, random intercept cross-lagged panel models (RI-CLPMs) provide the most rigorous test of causal predominance between 2 outcomes by quantifying the temporal association over multiple follow-up periods and by dissociating within-person and between-person variance.² Using this approach, we investigated year-to-year associations between cannabis use and PS over 4 years in youth aged 13 years at study onset.

Methods | This analysis capitalizes on the developmentally informed Co-Venture cohort,³ which includes 76% of all grade 7 students attending 31 secondary schools in the greater Montreal, Quebec, Canada, area, representing 15% of all schools in the area and each of their respective school districts in size and deprivation indexes within 1.5 SD. A total of 3966 adolescents actively assented to be part of the study and completed a confidential annual web-based survey from age 13 to 16 years involving self-report of past-year cannabis use and PS. Psychosis symptoms were assessed with the Adolescent Psychotic-Like Symptoms Screener,⁴ and cannabis use frequency was assessed with a 6-point scale (0 indicates never, and 5 indicates every day). The CHU Sainte-Justine Research Center ethics committee approved this research.

Reliability of substance use was evaluated using a sham drug item. Students with at least 1 data point were included in the analysis. A “missing completely at random test” using the R package “MissMech” (<https://CRAN.R-project.org/package=MissMech>) confirmed that the data were missing at random.

The RI-CLPM uses a multilevel approach to test for within-person differences that inform on the extent to which an individual’s increase in cannabis use precedes an increase in this individual’s PS (and vice versa).² The models were implemented in MPLUS 8 (<http://www.statmodel.com>), with $\alpha = .05$, using the full information maximum likelihood (FIML) method.

Results | The final sample included 3720 adolescents (mean [SD] age, 12.8 [0.4] years; 1828 [49.1%] female). A basic model containing only autoregressive paths, random intercepts, and within-time correlations across variables was first tested, followed by a transactional model that also contained cross-lagged associations (Figure). The χ^2 difference test favored the transactional model ($\Delta\chi^2_6 = 22.15$, $P = .001$).

The transactional model revealed statistically significant positive cross-lagged associations, at every time point, from cannabis use to PS reported 12 months later, over and above the random intercepts of cannabis use and PS (between-person differences). These cross-lagged associations were similar in size to the autoregressive link (annual stability) between PS from ages 15 to 16 years. Psychosis symptoms at age 15 years had a statistically significant positive association with cannabis use at age 16 years. All autoregressive links and within-time correlations at ages 14, 15, and 16 years were also statistically significant.

Discussion | This analysis demonstrates a predominant association at the individual level of cannabis use frequency with increased PS, and not the opposite, in the general population at a developmental stage when both phenomena have their onset. One limitation was that cannabis use and PS were not confirmed with clinician or collateral reports. However, previous work has shown positive predictive values ranging from 80% to 100% from 3 self-report items to identify interview-verifiable PS.⁵ Furthermore, self-report is the most efficient way to assess substance use when there are no consequences to reporting because collateral reports and biologic measures are not sensitive to the sporadic nature of adolescent substance use.⁶

Considering that PS are associated with risk for psychosis, as well as nonpsychotic disorders, these results emphasize the need for targeted cannabis use prevention as jurisdictions revise their cannabis regulatory policies. Promoting evidence-based interventions and policies that reduce access to and demand for cannabis among youth could lead to population-based reductions in risk for major psychiatric conditions.

Josiane Bourque, MSc
 Mohammad H. Afzali, PhD
 Patricia J. Conrod, PhD

Author Affiliations: Department of Psychiatry, University of Montreal, CHU Sainte-Justine Research Center, Montreal, Quebec, Canada.

Accepted for Publication: April 6, 2018.

Corresponding Author: Patricia J. Conrod, PhD, Department of Psychiatry, University of Montreal, CHU Sainte-Justine Research Center, 3175 Côte Ste-Catherine, Montreal, QC H3T 1C5, Canada (patricia.conrod@umontreal.ca).

Published Online: June 6, 2018. doi:10.1001/jamapsychiatry.2018.1330

Author Contributions: Ms Bourque and Dr Conrod had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Bourque, Conrod.

Critical revision of the manuscript for important intellectual content: Afzali, Conrod.

Statistical analysis: All authors.

Obtained funding: Conrod.

Administrative, technical, or material support: Conrod.

Study supervision: Conrod.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by grants FRN114887 and SH1155406 from the Canadian Institutes of Health Research. Ms Bourque was supported by a doctoral fellowship from the Canadian Institutes of Health Research, and Dr Conrod was supported by a senior investigator award from the Fonds de la Recherche du Québec en Santé.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

1. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophr Bull.* 2016;42(5):1262-1269.
2. Hamaker EL, Kuiper RM, Grasman RP. A critique of the cross-lagged panel model. *Psychol Methods.* 2015;20(1):102-116.
3. O’Leary-Barrett M, Mäse B, Pihl RO, Stewart SH, Séguin JR, Conrod PJ. A cluster-randomized controlled trial evaluating the effects of delaying onset of adolescent substance abuse on cognitive development and addiction following a selective, personality-targeted intervention programme: the Co-Venture trial [published correction appears in *Addiction*. 2018;113(3):581]. *Addiction.* 2017;112(10):1871-1881.
4. Laurens KR, Hodgins S, Maughan B, Murray RM, Rutter ML, Taylor EA. Community screening for psychotic-like experiences and other putative antecedents of schizophrenia in children aged 9-12 years. *Schizophr Res.* 2007;90(1-3):130-146.
5. Kelleher I, Harley M, Murtagh A, Cannon M. Are screening instruments valid for psychotic-like experiences? a validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophr Bull.* 2011;37(2):362-369.
6. Clark DB, Winters KC. Measuring risks and outcomes in substance use disorders prevention research. *J Consult Clin Psychol.* 2002;70(6):1207-1223.

CORRECTION

Incomplete Author Name Indexed: In the Original Article titled “Glucose Metabolism in Patients With Schizophrenia Treated With Atypical Antipsychotic Agents: A Frequently Sampled Intravenous Glucose Tolerance Test and Minimal Model Analysis,”¹ published in January 2005 in *JAMA Psychiatry* (then *Archives of General Psychiatry*), an incomplete author name was indexed. The fifth coauthor’s name should have been indexed as Evins AE instead of Evins E.

1. Henderson DC, Cagliero E, Copeland PM, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Arch Gen Psychiatry.* 2005;62(1):19-28.