INVESTIGATING CUMULATIVE MARIJUANA USE AND RISK OF CARDIOVASCULAR DISEASE IN MIDDLE AGE WITH LONGITUDINAL DATA

Never before have so many people expressed such strong interest in knowing the impact of marijuana legalization on human behavior and health.[1,2] There is a global trend toward legalizing marijuana. According to the National Organization for the Reform of Marijuana Laws, 29 US states permit marijuana use (http://norml.org/laws). However, research from diverse sources has produced mixed findings regarding the impact of marijuana laws.[3,4]

A recent *AJPH* article by Reis et al. addressed cumulative marijuana exposures and cardiovascular disease (CVD).[5] In this timely research, the authors used data from a long-established project (the Coronary Artery Risk Development in Young Adults [CARDIA] study), funded by the National Institutes of Health, in which cardiovascular events were determined via standard diagnostic procedures. Reis et al. used a Cox proportional hazards model and a trend test to assess the impact of marijuana exposures. However, we believe that their evidence is inadequate to conclude, as they did from their findings, that "[n]either cumulative lifetime nor recent use of marijuana is associated with the incidence of CVD in middle age."[5(p601)]

As an example, lifetime marijuana use is not a good measure for this purpose given that it is a compound indicator encompassing (1) those who use marijuana continuously after initiation, (2) those who quit after initiation, and (3) those who initiated use recently.[6] To illustrate this point, Table 1 summarizes results from the Reis et al. study. CARDIA's 26.9 years of follow-up with 5113 participants showed that 4286 were lifetime users, 827 had never used marijuana, and 960 were current users. These data indicate that 3326 of the 4286 (4286 − 960) lifetime users, or 77.6%, were ex-users. In other words, 77.6% of the Reis et al. figure on lifetime use is a reflection of the effect of quitting rather than using marijuana.

Reis et al. noted that self-reported marijuana exposure is subject to error. However, they derived a dosage measure by multiplying reported use in a given month by years of follow-up, amplifying the error. This may explain the inconsistent dose–response relationships reported. We conducted a quick analysis with a dichotomized measure of current marijuana use, and the results showed a cumulative relative risk for current marijuana exposure of 1.63 (95% confidence interval = 1.22, 2.19; $P < .01$).

On the basis of our observations, we recommend a reinvestigation of the same study hypotheses with alternative approaches, such as adding a group of former marijuana users to allow an exploration of the effects of quitting, using binary measures of marijuana exposure before searching for dose–response relationships, and implementing new methods of assessing long-term exposures (e.g., developmental trajectory analyses).[7] AJPH

Xinguang Chen, MD, PhD
Ding-Geng Chen, PhD
Bin Yu, MD, MPH

ABOUT THE AUTHORS

Xinguang Chen and Bin Yu are with the Department of Epidemiology, University of Florida, Gainesville. Ding-Geng Chen is with the School of Social Work, University of North Carolina at Chapel Hill.

Correspondence should be sent to Xinguang Chen, MD, PhD, Department of Epidemiology, University of Florida, 2004 Mowry Rd, CTRB #4228, Gainesville, FL 32610 (e-mail: jimax.chen@phhp.ufl.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This letter was accepted December 23, 2017.
doi: 10.2105/AJPH.2018.304307

CONTRIBUTORS

X. Chen drafted and revised the letter, D.-G. Chen conducted the data analysis and interpreted the results, and B. Yu contributed to the first draft of the letter and revised the final version.

REFERENCES

1. Cerdá M, Wall M, Feng T, et al. Association of state recreational marijuana laws with adolescent marijuana use. *JAMA Pediatr*. 2017;171(2):142–149.

2. Chen X, Yu B, Lasopa SO, Cottler LB. Current patterns of marijuana use initiation by age among US adolescents and emerging adults: implications for intervention. *Am J Drug Alcohol Abuse*. 2017;43(3):261–270.

3. Franz CA, Frishman WH. Marijuana use and cardiovascular disease. *Cardiol Rev*. 2016;24(4):158–162.

Letters to the editor referring to a recent *AJPH* article are encouraged up to 3 months after the article's appearance. By submitting a letter to the editor, the author gives permission for its publication in *AJPH*. Letters should not duplicate material being published or submitted elsewhere. The editors reserve the right to edit and abridge letters and to publish responses.

Text is limited to 400 words and 7 references. Submit online at www.editorialmanager.com/ajph. Queries should be addressed to the Editor-in-Chief, Alfredo Morabia, MD, PhD, at editorajph@qc.cuny.edu.

TABLE 1—Summary of Reis et al. Study Results

Type of Marijuana Use	Lifetime Users, No. (%)	Never Users, No. (%)	Total, No.
Lifetime	4286 (83.8)	827 (16.2)	5113
Current	960 (18.8)	4153 (81.2)	5113
Difference	3326 (77.6[a])	3326 (402.2[b])	0

Note. Current use indicates use prior to the diagnosis of a cardiovascular event or death.
Source. Data are from the study by Reis et al.[5]
[a]Quitters.
[b]Initiators.

4. Pacula RL, Powell D, Heaton P, Sevigny EL. Assessing the effects of medical marijuana laws on marijuana use: the devil is in the details. *J Policy Anal Manage*. 2015;34(1):7–31.

5. Reis JP, Auer R, Bancks MP, et al. Cumulative lifetime marijuana use and incident cardiovascular disease in middle age: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Public Health*. 2017;107(4):601–606.

6. Chen X, Li G, Unger JB, Liu X, Johnson CA. Secular trends in adolescent never smoking from 1990 to 1999 in California: an age-period-cohort analysis. *Am J Public Health*. 2003;93(12):2099–2104.

7. Nagin D. *Group-based Modeling of Development*. Cambridge, MA: Harvard University Press; 2005.

REIS ET AL. RESPOND

We thank Chen et al. for their letter. Chen et al. assert that lifetime use is not a "good measure" for investigating whether marijuana contributes to the development of cardiovascular disease (CVD). However, a recent report from the National Academies Committee on the Health Effects of Marijuana noted several important limitations of studies on marijuana use and CVD.[1] Two of these shortcomings are the reliance on only a single assessment of marijuana and the lack of studies on lifetime use. Our study estimated lifetime use based on information collected at up to eight assessments every two to five years over a 25-year period beginning in early adulthood, thereby addressing both limitations in the literature simultaneously. This methodology has been used in several studies published by our research group.[2–7]

Chen et al. state that "77.6% of the result by Reis et al. study on lifetime use is a reflection of the effect of quitting rather than using marijuana." We believe it is both inaccurate and misleading to use the percentage of former marijuana users in the cohort to explain why our findings mask any potential adverse effect of marijuana use on CVD. Lifetime use, by its very definition, estimates exposure over the entire course of one's lifetime regardless of the time period in which one was exposed. Thus, lifetime use is also estimated among former marijuana users.

Chen et al. seem to have taken the sample sizes in Table 2 to calculate a crude relative risk of CVD for recent users of marijuana. However, they did not account for the large number of factors, such as tobacco cigarette smoking, that may confound this association. When adjusted for the potential confounding factors listed in the footnote to Table 2, the adjusted hazard ratio comparing recent with no recent use was 0.96 (95% confidence interval = 0.64, 1.43). The authors suggest that future studies should examine the effect of quitting on CVD risk, but these results suggest little evidence for an association of recent marijuana use with incident CVD.

We concluded that neither cumulative lifetime nor recent use of marijuana is associated with the incidence of CVD. Because we were unable to directly address the question of whether marijuana may act as a trigger of acute coronary heart disease, we further concluded that potential marijuana users, particularly those at high risk, should be counseled about this potential concern. We believe these conclusions remain a valid reflection of our findings. AJPH

Jared P. Reis, PhD
Reto Auer, MD, MAS
Michael P. Bancks, PhD
David C. Goff, Jr., MD, PhD
Cora E. Lewis, MD, MSPH
Mark J. Pletcher, MD, MPH
Jamal S. Rana, MD, PhD
James M. Shikany, DrPH
Stephen Sidney, MD, MPH

ABOUT THE AUTHORS

Jared P. Reis and David C. Goff Jr are with the Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD. Reto Auer and Mark J. Pletcher are with the Department of Epidemiology and Biostatistics, University of California, San Francisco. Michael P. Bancks is with the Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL. Cora E. Lewis and James M. Shikany are with the Division of Preventive Medicine, Department of Medicine, University of Alabama, Birmingham. Jamal S. Rana and Stephen Sidney are with the Division of Research, Kaiser Permanente Northern California, Oakland.

Correspondence should be sent to Jared P. Reis, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, 6701 Rockledge Dr, Suite 10186, Bethesda, MD 20892 (reisjp@nhlbi.nih.gov). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This letter was accepted December 23, 2017.

Note. *The views expressed in this letter are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the US Department of Health and Human Services.*

doi: 10.2105/AJPH.2018.304308

CONTRIBUTORS

All authors contributed equally to this letter.

REFERENCES

1. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: National Academies of Sciences, Engineering, and Medicine; 2017.

2. Auer R, Vittinghoff E, Yaffe K, et al. Association between lifetime marijuana use and cognitive function in middle age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *JAMA Intern Med*. 2016;176(3):352–361.

3. Ishida JH, Auer R, Vittinghoff E, et al. Marijuana use and estimated glomerular filtration rate in young adults. *Clin J Am Soc Nephrol*. 2017;12(10):1578–1587.

4. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA*. 2012;307(2):173–181.

5. Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *Am J Cardiol*. 2006;98(4):478–484.

6. Auer R, Sidney S, Goff DC, et al. Lifetime marijuana use and subclinical atherosclerosis: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Addiction*. 2017;Epub ahead of print November 22, 2017.

7. Bancks MP, Auer R, Carr JJ, et al. Self-reported marijuana use over 25 years and abdominal adiposity: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Addiction*. 2017;Epub ahead of print November 11, 2017.