COMMENTARY

The Importance of Methodological Meta-Analyses and a Call to Assess Current and Former Drinking Patterns: A Commentary on Stockwell et al. (2016)

I commend the authors for this valuable review (Stockwell et al., 2016—this issue), which updates and extends earlier work (Fillmore et al., 2006) using state-of-the-art meta-analytic methods and following the PRISMA guidelines. Importantly, theory-driven methodological design problems are analyzed as study-level characteristics. These are then sequentially excluded to investigate the role of mixing former drinkers, occasional drinkers, and lifetime abstainers in reference groups (i.e., abstainer reference group bias)—a common deficiency in all-cause mortality studies. Results focus us again on the quality of the widely circulated evidence that low-dose alcohol confers cardiovascular protection sufficient to lower all-cause mortality. Indeed, some recent systematic reviews and meta-analyses have again emphasized such protection (Ronksley et al., 2011). In Ronksley et al., although a sensitivity analysis examined former drinkers versus nondrinkers in a subset of studies permitting this for cardiovascular mortality and for coronary heart disease mortality, the authors' methods do not permit strong conclusions about degree of bias introduced when studies are combined, as they are in their primary analyses. Addressing degree of bias is the particular contribution of the present meta-analysis because this is its explicit aim (Stockwell et al., 2016).

Further emphasizing the importance of methodologically driven work like this, the belief in protective effects of moderate drinking is sufficiently widely held to have been incorporated into global burden of disease estimates (e.g., Lim et al., 2012), and we are beginning to see renewed calls from certain medical commentators to prescribe moderate drinking for lifelong nondrinkers of ages about 40 to 50 (Rubin, 2014). Offering medical advice like this, I believe, is premature, and I have strongly opposed this on a number of grounds, including methodological weaknesses in numerous epidemiological studies (studied anew in this meta-analysis) marshaled as evidence of reductions in cardiovascular disease and all-cause mortality (Greenfield & Kerr, 2014). These methodological weaknesses often involve the inability to accurately specify lifetime abstainers as a reference category or separate this group from former heavy drinkers.

The conclusions of the present meta-analysis (Stockwell et al., 2016—this issue) re-emphasize that the widespread design problem of including former drinkers in the abstainer reference group will magnify the apparent health benefits of moderate intake. The meta-analysis notes that “of 87 studies identified, 65 included former drinkers in the ‘abstainer’ reference group” (Stockwell et al., p. 194). In addition, 50 included occasional drinkers in this group, leaving only 13 studies without either bias. (It would be useful to re-analyze from the same perspective the set of 84 studies of selected cardiovascular disease outcomes included in the Ronksley et al. [2011] meta-analysis—see also Brien et al. [2011].)

Kerr and I (Greenfield & Kerr, 2014) have argued further that doctors or medical assistants attempting to quickly assess whether a patient is a lifetime abstainer (and so a target of the ill-founded drinking advice) will likely encounter the same ascertainment problem seen in studies involving lifetime abstainer groups. We know from panel surveys that many respondents who later report never in their lives having drunk alcohol reported at earlier interviews that they were then prior or current drinkers (Caldwell et al., 2006; Rehm et al., 2008). In addition, no research to my knowledge has yet studied drinking behavior outcomes in the clearly heterogeneous group who would state in a medical assessment that they never were drinkers following advice from their doctor to “relax and take a drink a day, preferably with dinner” (Rubin, 2014, p. 2890). Methodological work on claiming never to have drunk alcohol in even “neutrally framed” panel surveys results in false lifetime abstention answers (Rehm et al., 2008), and questions from a medical authority figure could lead to even more denial of former drinking. An experimental trial of screening, followed by advice/no advice, can readily be envisioned, but would such a trial clear a well-informed human subjects review, given the uncertainties of outcomes and potential risks to participants in the intervention arm, given that such advice could translate into heavy per occasion or even dependent drinking?

Relevant too is the finding from the Stockwell et al. (2016) meta-analysis that in all the pooled models, occasional drinkers had lower mortality risks than low volume

drinkers. Occasional drinkers were defined as drinking less than 1.3 g/day (or about a standard drink every 10 days on average), whereas low volume was defined as this level up to 25 g/day (the volume level often termed *moderate drinking*). Moderate rather than occasional drinking is believed to engage biological mechanisms conferring coronary artery protection, such as those that elevate high-density lipoprotein cholesterol levels. A recent meta-analysis of intervention studies found effects of drinking alcohol on several cardiovascular disease–related biomarkers, including a dose-response relationship with high-density lipoprotein cholesterol (vs. not drinking; Ronksley et al., 2011).

To really resolve the controversy, we need more high-quality prospective mortality studies. I would further urge that future studies address drinking pattern, ideally with baseline measures including life-course heavy drinking assessments (Greenfield et al., 2014), because heavy drinking can and does occur at low volume levels, considerably affecting mortality (Rehm et al., 2006; Roerecke et al., 2011). Absent life-course heavy drinking measures, volume-based mortality studies will remain inherently limited.

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References

Brien, S. E., Ronksley, P. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. (2011). Effect of alcohol consumption on biological markers associated

- with risk of coronary heart disease: Systematic review and meta-analysis of interventional studies. *BMJ*, 342, d636. doi:10.1136/bmj.d636.
- Caldwell, T. M., Rodgers, B., Power, C., Clark, C., & Stansfeld, S. A. (2006). Drinking histories of self-identified lifetime abstainers and occasional drinkers: Findings from the 1958 British Birth Cohort Study. *Alcohol and Alcoholism*, 41, 650–654. doi:10.1093/alcac/agl088.
- Fillmore, K. M., Kerr, W. C., Stockwell, T., Chikritzhs, T., & Bostrom, A. (2006). Moderate alcohol use and reduced mortality risk: Systematic error in prospective studies. *Addiction Research & Theory*, 14, 101–132. doi:10.1080/16066350500497983.
- Greenfield, T. K., & Kerr, W. C. (2014). Physicians' prescription for lifetime abstainers aged 40 to 50 to take a drink a day is not yet justified. *Alcoholism: Clinical and Experimental Research*, 38, 2893–2895. doi:10.1111/acer.12582.
- Greenfield, T. K., Nayak, M. B., Bond, J., Kerr, W. C., & Ye, Y. (2014). Test-retest reliability and validity of life-course alcohol consumption measures: The 2005 National Alcohol Survey follow-up. *Alcoholism: Clinical and Experimental Research*, 38, 2479–2487. doi:10.1111/acer.12480.
- Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., . . . Ezzati, M. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, 380, 2224–2260. doi:10.1016/S0140-6736(12)61766-8.
- Rehm, J., Greenfield, T. K., & Kerr, W. (2006). Patterns of drinking and mortality from different diseases—an overview. *Contemporary Drug Problems*, 33, 205–235.
- Rehm, J., Irving, H., Ye, Y., Kerr, W. C., Bond, J., & Greenfield, T. K. (2008). Are lifetime abstainers the best control group in alcohol epidemiology? On the stability and validity of reported lifetime abstinence. *American Journal of Epidemiology*, 168, 866–871. doi:10.1093/aje/kwn093.
- Roerecke, M., Greenfield, T. K., Kerr, W. C., Bondy, S., Cohen, J., & Rehm, J. (2011). Heavy drinking occasions in relation to ischaemic heart disease mortality—an 11–22 year follow-up of the 1984 and 1995 US National Alcohol Surveys. *International Journal of Epidemiology*, 40, 1401–1410. doi:10.1093/ije/dyr129.
- Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. (2011). Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. *BMJ*, 342, d671. doi:10.1136/bmj.d671.
- Rubin, E. (2014). To drink or not to drink: That is the question. *Alcoholism: Clinical and Experimental Research*, 38, 2889–2892. doi:10.1111/acer.12585.
- Stockwell, T., Zhao, J., Panwar, S., Roemer, A., Naimi, T., & Chikritzhs, T. (2016). Do “moderate” drinkers have reduced mortality risk? A systematic review and meta-analysis of alcohol consumption and all-cause mortality. *Journal of Studies on Alcohol and Drugs*, 77, 185–198. doi:10.15288/jsad.2016.77.185.