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Invited Commentary

Invited Commentary: Never, or Hardly Ever? It Could Make a Difference

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A paper showing that about one half of persons stating lifelong alcohol abstinence had previously reported drinking (*Am J Epidemiol* 2008;168(8):866—871) reopens debate about the validity of this frequently used referent group in alcohol-health studies. Misclassification of lifelong abstainers could result in underestimation of harmful effects of heavy drinking and overestimation of benefits of lighter drinking. Imprecise and unreliable ascertainment of alcohol intake is the rule in the area of alcohol epidemiology research. However, inaccurate ascertainment of past infrequent drinking may have less effect upon outcome estimates than the consequences of other measurement errors such as underreporting of intake. Communication about alcohol-health relations would be improved if all research reports explicitly described queries and methods by which alcohol intake was categorized and if limitations were always frankly acknowledged.

alcohol drinking; control groups; data collection; longitudinal studies; reproducibility of results

DEFINING ''NEVER''

CAPTAIN: And I'm never, never sick at sea.
CHORUS: What, never?
CAPTAIN: No, never.
CHORUS: What, *never*?
CAPTAIN: Well, *hardly ever*!
Gilbert and Sullivan, *HMS Pinafore*, 1878

As alcohol epidemiology matures, it is becoming more sophisticated. A fine example is provided in this issue of the *Journal* by Rehm et al. (1), who present data that raise questions about the accuracy of reports of lifelong alcohol abstinence. The authors first remind us of the special importance of a valid reference group and of the need to separate current nondrinkers and former drinkers because of the ''sick-quitter'' phenomenon (2). Their data (1) show that about half of ''lifelong abstainers'' in a national US sample had previously reported ingestion of some alcohol beverage, a proportion similar to that in a British survey (3). Most had been infrequent light drinkers, but some had previously reported substantial alcohol intake. This discrepancy raises the issue of whether use of ''lifelong abstainers'' as a referent group in alcohol epidemiology work represents flawed methodology. Based upon a previously published meta-analysis (4), Rehm et al. estimate that alcohol-attributable all-cause mortality might be underestimated by 2%–15% in men and 2%–22% in women. The upper limits of these estimated errors are far from trivial. A suggested more ''ideal'' referent might be composed of persons who repeatedly report no drinking or very light drinking.

The Gilbert and Sullivan excerpt that heads this commentary is not meant to trivialize the issue. After denying seasickness twice, the captain concedes only when confronted by evident skepticism. It is implied that ''hardly ever'' minimized his seasickness history. Is such persistent skeptical questioning possible or even appropriate for epidemiologic data collection? Would institutional review boards allow it? Feasibility for a large population would be problematic. However, the captain's seasickness history is analogous to alcohol history data.

The Rehm et al. paper (1) is valuable in pointing out yet again that categorization of alcohol intake information is intrinsically imprecise. The authors are correct when stating that multiple measures yield more valid alcohol intake data than single ones. Habits do change, but, even without changes, many persons will give different responses at various times. The unfortunate truth is that alcohol epidemiology researchers usually must deal with ambiguously defined and reported information about amount of alcohol intake. Problems related to definitions, misinterpretation of queries,

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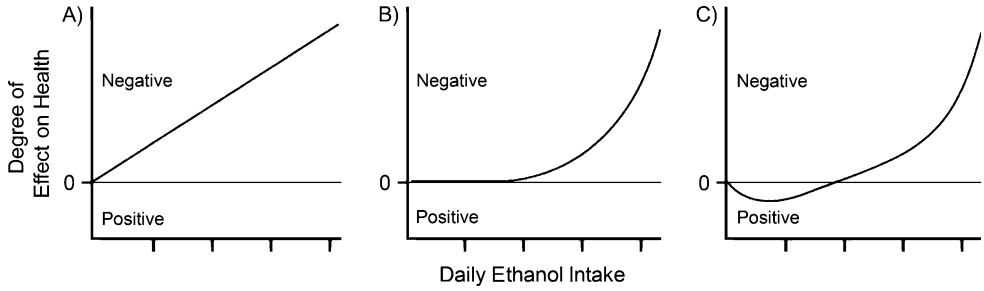

Figure 1. Three hypothetical alcohol-health associations, representing linear (panel A), threshold (panel B), and J-curve (panel C) relations. A linear relation might occur between amount of alcohol ingested and blood alcohol levels. A threshold relation is probably present between alcohol intake and several individual outcomes (e.g., liver cirrhosis); this part of the figure shows no apparent effect below the threshold dose but an exponentially increasing effect above the threshold. Panel C illustrates a J-curve (e.g., alcohol and total mortality) with an apparent beneficial effect below a threshold and an exponentially increasing effect above the threshold.

deliberate underreporting, averaging of variations in consumption, and ranges within categories are only the beginning. Reported outcomes may be related to recent drinking or to lifetime intake. Problems multiply if one wishes to consider measurement of consumption of specific beverage types (beer, liquor, wine, and subtypes of all). We usually hope that the proportion of persons reporting something close to accurate intake is sufficient to enable meaningful comparisons between reported categories.

HISTORICAL PERSPECTIVE

Adverse medical and social consequences of heavy drinking, in either a steady or a binge pattern, have been evident for millennia. Prior to the mid-20th century, reports often adopted a relatively uncritical attitude about methodology in studies regarding outcomes related to heavy drinking. Acceptance that association indicated causality was sometimes accompanied by overreadiness to accept sole causality. The widespread perception that there was a threshold alcohol dose for harm led to postulation of a ''sensible'' if not quite ''safe'' limit. Many readers will recall ''Anstie's Sensible Limit'' of 45 mL of ethyl alcohol per day, proposed in 1862 (5). Without population data, and realizing the existence of much individual variation in alcohol tolerance, Anstie must have based his suggested limit on commonsense observation. In keeping with the culture of the times, and well before the invention of the motor vehicle, Anstie intended his sensible limit primarily for mature men, not for women or youths.

In recent decades, evidence of lower risk among lighter drinkers than among abstainers, most notably for atherothrombotic vascular disease (6, 7), has coincided with an intense examination of study methodology (1, 2, 8). Consistency in studies (6, 7), relative specificity for atherothrombotic disease, and plausible biologic mechanisms (9, 10) create a case for a causal explanation for the inverse relation of alcohol drinking to vascular disease. Residual skepticism was fueled by the realization that some earlier studies failed to separate former drinkers, including ''sick quitters,'' from lifelong abstainers, thus exaggerating the apparent benefit of lighter drinking. Studies using variously defined ''lifelong abstainers'' as the referent have confirmed apparent protection (7), but the absence of prospective randomized trials with cardiovascular events as the outcome allows residual uncertainty about unresolved confounding. Fear that encouragement of drinking will cause problems in some persons contributes to reluctance by some to accept that there is any benefit from alcohol. Rehm et al. (1) ''strongly caution'' against using reported lifetime abstainers as a comparison group; this statement will raise further questions about the validity of reported observational studies.

PERSONAL PERSPECTIVE

Personal experience cannot fail to modulate one's perceptions. Thirty years ago, I was involved in construction of a check-sheet questionnaire about alcohol habits, with time constraints limiting the number of potential queries. On the basis of anecdotal experience in talking with patients as well as a belief that infrequent alcohol intake was not likely to have biologic effects, lifelong abstainers were defined as noncurrent drinkers who reported having ''no alcoholic beverages during the past year'' and ''never or almost never before the past year.'' A current infrequent drinker category was created by the option ''less than 1 (drink) per month (special occasions only).'' It was hypothesized that these infrequent drinkers could serve as an alternate referent to ''lifelong abstainers.'' It turned out that infrequent drinkers outnumbered both lifelong abstainers and past drinkers. Among 56,926 men, 7.2% were lifelong abstainers, 4.2% former drinkers, and 14.2% infrequent drinkers; among 72,008 women, these proportions were 15.8% lifelong abstainers, 2.5% former drinkers, and 26.8% infrequent drinkers.

In analyses of various outcomes, including total mortality (11, 12), we found no or trivial differences in risk between persons classified as infrequent drinkers and those classified as lifelong abstainers. In total mortality data through 2002

(12), with 21,535 deaths among the 128,934 men and women, adjusted hazard ratios for total mortality (vs. ''lifelong abstainers'') were 1.19 (95% confidence interval: 1.10, 1.27) for former drinkers and 0.98 (95% confidence interval: 0.93, 1.02) for infrequent drinkers. The trivial difference between infrequent drinkers and abstainers provides no support for the suggestion that lifelong abstainers have a spuriously increased risk related to inclusion of some actual past drinkers.

Probably all would agree that it is implausible that a few drinks in the remote past are likely to affect current health. By analogy, does smoking a few tobacco cigarettes in adolescence (traditionally behind the barn) make one, for health risk purposes, a former smoker? However, persons who infrequently had indulged in 1 or more drinking binges could, with honesty, include themselves among ''almost never'' drinkers or among current infrequent drinkers. Persons with such a history are at greater risk of future heavy drinking. Except for this important problem, do rare, remote binge episodes play a role in later biologic effects of alcohol? The answer is not clear. One evident conclusion is that a complete alcohol history requires much detail about current and lifetime habits.

OTHER PROBLEMS

In the present paper (1), it is interesting that ''consistent lifelong abstainers'' (vs. ''inconsistent abstainers'') were more likely to be older, female, and Hispanic. In addition, most inconsistent abstainers experiencing past heavy drinking episodes were members of ethnic minority groups. What inhibits these persons from stating their past drinking? Could perceived attitudes of interviewers, especially nonminority interviewers, be a factor? Could lower mean educational status be a factor? Would persons violating religious or moral prohibitions be more likely to give inconsistent responses? Determination of inconsistent lifelong abstainer was assessed among persons who first indicated having a drink in the last 12 months. Then they received a present-tense alcohol frequency question, How often do you have any type of beverage containing alcohol?, coupled with choice of the 11th option, I have never had any kind of beverage containing alcohol. Is it possible that the incompatibility between present and past tense, together with the tricky syntactic structure ''have never had,'' confused some subjects? Minor changes in query wording can affect responses.

Imprecise alcohol data lead to imprecision in derived estimations such as attributable risks or threshold levels for observed effects. One desired benefit of alcohol epidemiology is the ability to estimate lower limits of thresholds for risk and upper limits for relative safety or possible benefit. Aggregate thresholds are problematic because of individual variability. Imprecise categorization of alcohol intake in alcohol studies is another major issue. A pervasive factor is underreporting of intake by heavy drinkers, which is generally assumed to be common. Figure 1 shows 3 hypothetical alcohol-health associations: linear (panel A), threshold (panel B), and J-curve (panel C). With a true linear adverse alcohol-health effect, underreporting, by placing some heavy drinkers in lighter-drinking categories, exaggerates the adverse effect of lighter intake. With a threshold relation, the threshold is lowered or obliterated. With a J-curve, underreporting lessens the apparent benefit. Possible effects of underreporting have been shown in a cross-sectional analysis of systemic hypertension (13) and a prospective study of mortality (12).

A NEW PROBLEM

Public knowledge of potential benefit has become a potential factor in alcohol epidemiology. Even with a superbly accurate alcohol history database, future population studies will face a problem of bias related to drinking for health. A recently reported survey (14) indicated that almost one third of participants in the Boston, Massachusetts, area said that health benefits were a factor in their drinking. Thus, new studies will need to control for a ''sick new drinker'' effect, created by persons who started or increased alcohol intake because of existing illness or symptoms. An opposite bias might be introduced by low-risk persons who began drinking as part of an overall favorable health style. Researchers need to know reasons for drinking as well as for abstaining.

CONCLUSION

Like most creative research, the work of Rehm et al. (1) adds to our knowledge and simultaneously stimulates thoughts and questions. One obvious lesson is that we need better instruments to measure alcohol intake histories. Another is that complete description of methodology greatly aids evaluation and comparison of reports. Alcohol researchers can perform an important service by presenting verbatim expositions showing exactly how all information was obtained and how alcohol consumption was categorized. Such specificity, accompanied by frank discussion of implications and limitations, would move us in the right direction.

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