

## Alcohol intake, morbidity, and mortality

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This is an era in which we are increasingly concerned about the quality of the air that we breathe and the food that we eat. Alcohol, a beverage that has pleased our species for millennia, is one of the “foods” the consumption of which, in the words of the immortal bard, should give us pause. In this editorial, we express our concerns on the subject through a presentation and discussion of the results of two large epidemiological studies<sup>1,2</sup> published nearly two decades apart.

A voluminous body of literature shows that men and women who consume alcohol regularly have higher death rates from accidental injury, violence, suicide, poisoning, cirrhosis of the liver, cancer, and, possibly, hemorrhagic stroke. Much literature also supports the view that men and women who regularly drink have lower death rates from coronary heart disease and thrombotic stroke. What is the net impact of these favorable and unfavorable alcohol-mediated effects on persons with regular alcohol intake? Because the incidence of different alcohol-related events varies between men and women, across age groups, and across other sociodemographic and clinical categories, it is evident that any study of the balance of risk will need to take subpopulations into account. The subject was addressed in a large epidemiological study, described by Thun *et al.*<sup>1</sup> in 1997.

The sample in this study<sup>1</sup> comprised nearly half a million Americans, aged 30 years or more, who provided complete information about smoking and drinking habits. There were totally 238,206 men and 251,420 women aged 30–104 years (mean, 56 years). About 98% of these men and women could be followed for up to 9 years, during which period 12% died. Death certificates were obtained for all but 2% of those who died.

In this study, alcohol consumption was assessed at baseline and at endpoint using questionnaires, and was categorized as none, less than daily but at least thrice a week, 1 drink per day, 2–3 drinks per day, and 4 or more drinks per day. For operational purposes, one drink was considered as 12 g of absolute alcohol; in common parlance, this amounts to about one small peg (30 ml) of 75° proof liquor.

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On the surface, it appears that this classification is somewhat unsatisfactory on several counts; more useful quantitative indices, for example, might have been average daily consumption of absolute alcohol, lifetime consumption of absolute alcohol, and quantity of absolute alcohol consumed per drinking occasion. However, such indices can be reliably calculated only from data obtained through direct interview; furthermore, such quantitative indices may not be helpful when the relationship between alcohol consumption and mortality variables is nonlinear (as actually transpired for several variables in the study). Therefore, considering the epidemiologic nature of the investigation, the investigators<sup>1</sup> did the best that was possible under the circumstances.

After excluding from analysis former drinkers and those with baseline cancer or cirrhosis, it was discovered that the results, in general, supported existing literature:

- In men, consumption of alcohol was associated with significantly increased risk of mortality due to the following: Cirrhosis, alcoholism, or both; injuries and external causes; alcohol-related cancers (mouth, esophagus, pharynx, larynx, liver); colorectal cancer; all other cancers
- In women, consumption of alcohol was associated with significantly increased risk of mortality due to the following: Cirrhosis, alcoholism, or both; alcohol-related cancers; breast cancer. Risks of death due to colorectal cancer, all other cancers, injuries, and external causes were not significantly elevated
- In both sexes, consumption of alcohol was found to significantly decrease the risk of mortality due to the following: Coronary heart disease when there was no disease preexisting; coronary heart disease when such disease did preexist; stroke; other circulatory disease; all cardiovascular disease; all other causes. In persons with preexisting coronary heart disease and with the diagnosis of stroke, benefits with alcohol were evident at all levels of consumption for women, but only with moderate consumption in men.

Thun *et al.* presented relative risk data for each mortality variable in each drinking category for men and women separately. A few interesting observations were:

- The risk of death due to all cardiovascular disease was lowered by 30% (in men) to 40% (in women) in persons

who consumed at least, one drink a day, as compared with nondrinkers

- The risk of death due to breast cancer was 30% higher in women who consumed at least one drink a day, as compared with women who did not drink
- Most important of all, the risk of death from all causes was 20% lower in persons who consumed one drink a day, as compared with nondrinkers; above one drink per day, the advantage associated with alcohol intake was progressively attenuated.

Study participants were grouped into those at low and high cardiovascular risk. The former group reported no heart disease, hypertension, stroke, or diabetes mellitus at baseline; the latter group reported at least one of these conditions. Multivariate-adjusted death rates from all causes were calculated for both sexes. Important outcomes were:

- In low-risk subjects aged 30–60 years, one drink a day or less was associated with a lowered risk of death by about 10%, in comparison with not drinking at all; in contrast, 4 drinks a day or more increased the risk of death by 20%
- In high-risk subjects aged 30–60 years, 3 drinks a day or less was associated with a lowered risk of death by 10–20%, in comparison with not drinking at all
- In low-risk subjects aged 60–79 years, 3 drinks a day or less was associated with a lowered risk of death by 10–20%, in comparison with not drinking at all
- In high-risk subjects aged 60–79 years, drinking at all levels was associated with a lowered risk of death by 20%, in comparison with not drinking at all.

Thus, the most parsimonious conclusion is that, in middle-aged subjects and especially in those at low risk of cardiovascular disease, moderate consumption of alcohol (e.g. 1 drink per day) is associated with moderate reduction in the risk of mortality while high consumption (e.g. 4 drinks per day) is associated with moderately increased risk. As age and risk of cardiovascular disease increase, higher levels of alcohol consumption also appear to moderately protect against death.

Smokers, defined as those smoking at least a pack a day, were compared with nonsmokers. In both men and women aged 35–69 years, continued smoking approximately doubled the risk of death. Because persons who consume alcohol commonly smoke, as well, clinicians who counsel patients about drinking habits should also offer guidance about smoking habits.

This study<sup>[1]</sup> has several limitations. An obvious limitation is that the findings are applicable predominantly to middle-class, mostly Caucasian subjects aged 30 years and older; it is uncertain to what extent these findings can be generalized to, say, Indian patients in different socioeconomic strata. And, before adopting a benign

attitude towards moderate drinking in certain categories of persons, such as middle-aged men who are at cardiovascular risk, readers would do well to keep another important limitation in mind: Thun *et al.*<sup>[1]</sup> studied only mortality data, not morbidity data. It is known that even moderate alcohol consumption may result in psychosocial or medical morbidity and hence impaired quality of life. Furthermore, such morbidity may impact on mortality statistics in follow-up periods which exceed that described by Thun *et al.*<sup>[1]</sup> Other unknowns are the duration for which a subject must drink to experience the benefit of reduced risk of death and the duration for which this benefit continues after cessation of drinking. Finally, as will be reemphasized at the end of this article, the benefits associated with alcohol intake need not be causal; for causality to be attributed, randomized controlled trials are necessary, and none has so far been conducted.

There have been plenty of subsequent observational studies on health outcomes associated with alcohol intake, and reviews and even meta-analyses of the data have been published. One large and very recent study, published by Smyth *et al.*<sup>[2]</sup> in 2015, merits attention. The data were obtained from the Prospective Urban Rural Epidemiological study, which recruited participants from 12 countries (differing in income levels) in 5 continents; in this regard, therefore, the study<sup>[2]</sup> was more representative than the previously discussed study.<sup>[1]</sup>

The sample in this study<sup>[2]</sup> comprised 114,970 persons, aged 35–70 years, without a baseline history of heart disease, stroke, or cancer. Of these, 12,904 (11%) were from high-income countries (Sweden, Canada), 24,408 (21%) were from upper-middle income countries (Argentina, Brazil, Chile, Poland, South Africa, and Turkey), 48,845 (43%) were from lower-middle income countries (China, Columbia), and 28,813 (25%) were from low-income countries (India, Zimbabwe). The study, however, was not designed to be nationally representative.

Current drinking (at baseline) was reported by 36,030 (31%) persons; never drinkers comprised 65% of the overall sample, and 4% were former drinkers. The mean age of the current drinkers was 47–53 (mean, 50) years in different country groups. This sample was as little as 4% female in low-income countries to as much as 52% female in high-income countries (mean, 34%). High-level drinking (8% of current drinkers) was defined as >14 drinks per week in women and >21 drinks per week in men. Heavy episodic drinking (13% of current drinkers) was defined as 5 or more drinks per occasion at least once a month.

The sample was followed up for a median of 4.3 (interquartile range, 3.0–6.0) years. Cox proportional hazards regression was used to study associations with mortality ( $n = 2723$ ), cardiovascular disease ( $n = 2742$ ), myocardial infarction

( $n = 979$ ), stroke ( $n = 817$ ), alcohol-related cancer ( $n = 764$ ), injury ( $n = 824$ ), admission to hospital ( $n = 8786$ ), and for a composite of these outcomes ( $n = 11,963$ ). Never drinkers constituted the reference group. There were several important findings:

- Low-income countries had the lowest prevalence of current drinking but the highest prevalence of high intake and heavy episodic drinking
- Current (but not former) drinking was associated with reduced myocardial infarction (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63–0.93). This benefit, however, was absent in those with high intake, and those who were heavy episodic drinkers. Interestingly, this benefit was only observed for wine drinkers, and not for those who drank other forms of alcohol
- Current drinking was associated with an increased risk of alcohol-related cancers (HR, 1.51; 95% CI, 1.22–1.89) and injury (HR, 1.29; 95% CI, 1.04–1.61). Drinking behavior did not influence stroke or hospitalization risks
- High (but not low or moderate) alcohol intake was associated with increased mortality (HR, 1.31; 95% CI, 1.04–1.66). Heavy episodic drinking was also associated with increased mortality (HR, 1.54; 95% CI, 1.27–1.87)
- In current drinkers, the risk of the composite outcome was reduced in high and upper middle-income countries (HR, 0.84; 95% CI, 0.77–0.92) but not in the lower middle and low-income countries (HR, 1.07; 95% CI, 0.95–1.21). The difference in hazards was statistically significant ( $P < 0.0001$  for the interaction).

This study<sup>[2]</sup> suggests several important conclusions. Alcohol intake is associated with a reduced risk of myocardial infarction; however, this benefit is absent in high intake drinkers and in heavy episodic (binge) drinkers. Alcohol intake is associated with an increased risk of other adverse outcomes, including injury and cancer. High and heavy episodic intake are associated with an increased risk of death. Interestingly, the net effect of alcohol intake is to reduce adverse health outcomes, but this benefit is small and is statistically significant only in upper middle and high-income countries.

Of note, in this study,<sup>[2]</sup> some relationships, such as between high intake drinking or heavy episodic drinking and cancer or injury were not statistically significant. This is because the analyses were underpowered. That is, there were too few events/cases in these groups. Readers are referred to the original article for a detailed exposition of all the findings in all the relationships examined. Also, although the findings adjusted for potential confounders, cause-effect relationships cannot be conclusively stated, as with the beneficial effects of wine on the risk of myocardial infarction (unmeasured and unadjusted confounders could

be responsible for the outcomes). The findings of this study are applicable for an approximately 4 years follow-up period. We do not know whether the findings will change or whether new findings will emerge across a longer follow-up period. The findings of this study are also susceptible to a cohort effect; the results could change as healthcare practices change, such as when low-income countries become better developed.

What do these and other studies of a similar nature tell us? They provide hard epidemiological evidence that how people drink affects outcomes. For example, low levels of intake are associated with lower risk of myocardial infarction whereas binge drinking is associated with a range of adverse outcomes. Drinking to intoxication is associated with injury. Longer duration of drinking is associated with increased cancer risk. Importantly, there is no evidence that in people who do not drink, initiation of alcohol intake improves health outcomes, whereas evidence exists that reduction in alcohol intake in alcohol-dependent subjects reduces mortality risk.<sup>[3]</sup> These messages need to be communicated to populations at risk. The take home message is that alcohol intake is a major modifiable risk factor for morbidity and mortality in several fields of medicine.

## REFERENCES

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