Alcohol is a major environmental hazard, with negative effects on many organs, including the brain, liver, pancreas, and heart. It is a leading cause of mortality in industrialized countries. Whether the mortality effects of alcohol are due to genetic or environmental effects or a combination of both is poorly understood.

For example, cardiovascular and nearly all of the other alcohol-associated somatic disorders carry their own genetic vulnerability, and there is evidence that genetic variants associated with decreased alcohol intake may also be associated with decreased cardiovascular risk, irrespective of the degree of alcohol consumption. Persons with alcohol use disorders (AUDs) may also die because of consequences of comorbid tobacco and illicit drug use, which again carry their own genetic risk factors. Indeed, in patients with AUDs, tobacco-related mortality accounts for up to half of the deaths observed over a 12-year period following alcohol detoxification.

Road traffic crashes and suicides represent a significant cause of mortality in AUD. In addition, about half of all murders in the United States and Germany are committed under the influence of current alcohol intake, and elevated rates of alcohol-associated aggression are found in individuals with higher alcohol intake and hence also in those with AUDs, particularly if violent acts have been experienced during previous states of alcohol intoxication. Finally, socioeconomic status has been shown to moderate the risk for alcohol-related mortality across European countries; especially in younger adults of low socioeconomic status, alcohol-related deaths account for a large portion of excess mortality. These examples paint a complex picture of interrelated causality governed by both genetic and environmental risk factors for alcohol-related mortality rates.

The study by Kendler and coauthors in this issue of JAMA Psychiatry disentangles the environmental and genetic risk factors that contribute to increased mortality among individuals with AUDs. The authors studied all individuals born in Sweden from 1940 to 1965 and controlled for mortality rates in half-siblings, full-siblings, and monozygotic twins. They observed that familial factors significantly contributed to the rather strong increase in the mortality hazard ratio associated with AUDs in early to middle adulthood. In contrast, both increasing age and increasing duration of alcohol use contributed to high alcohol-associated mortality rates in late adulthood. In fact, Kendler and coauthors observed that AUD was associated with a 6-fold increase in mortality rate (5.8-5.9) for all ages and was highest in the age group of 30 to 39 years, showing an inverted U-shape and hence being lower in the age groups of 15 years and older and 65 years and older. Because all-cause mortality increases with age, most persons with AUDs will die with increasing duration of alcohol use. But when compared with the general population, mortality differences are most dramatic in early to middle adulthood.

In light of such observations, it is important to disentangle genetic and environmental risk factors both in middle adulthood (when AUDs cause the strongest increase in mortality rates) and in elderly individuals (when overall mortality is highest). Accordingly, the main goal of the current study was the question: do increased mortality rates in individuals with AUD arise from familial risk factors or from general effects of excessive alcohol intake? Familial contributions to high mortality rates do not necessarily imply genetic risk factors. However, the authors carefully weighed the evidence for the genetic contribution in early to middle adulthood and emphasized that the comparison of mortality rates associated with AUDs in half-siblings reared together vs apart support the hypothesis that increased mortality during early to middle adulthood mainly reflects the influence of genetic factors. The authors suggested that impulsivity and novelty seeking could be among such factors, as such personality traits are partly heritable and may contribute to the use of other illicit drugs and to increased risk-taking behavior and individual vulnerability to experience violence. This is of particular interest because several adoption studies and 1 twin study showed that there was no genetic contribution to violent behavior except in combination with AUDs. Therefore, further studies on specific causes of mortality associated with AUDs in early to middle adulthood and their association with risk taking and violent experiences are highly warranted.

There is a multitude of other, partially heritable risk factors associated with alcohol use, which can contribute to increased mortality in early to middle adulthood. Of specific importance is nicotine consumption, which is all too often associated with excessive alcohol intake and AUDs. Indeed, as indicated here, tobacco consumption accounts for up to 50% of elevated mortality rates following alcohol detoxification treatment in a community sample, thus pointing to nicotine dependence as another partially heritable risk factor, which can help to explain how genetic factors contribute to alcohol-associated mortality.

The study by Kendler and coauthors highlights several key points for further study. Exploration of International Classification of Diseases codes for causes of death may stimulate research in the widely understudied area of alcohol-related aggression, the role of comorbid drug consumption (eg, tobacco), and other environmental and social risk factors. Sex differences in AUDs are an understudied research area, and
the examination of causes of death in different age groups according to sex and AUDs is a topic of high importance for public health. Finally, the decreasing effect of familial and hence genetic factors in elevated mortality associated with AUDs emphasizes the need to address harmful alcohol use in the aging population: campaigns to prevent or reduce alcohol use are too often focused on young adults while neglecting elderly individuals. We hope that the study by Kendler and coauthors\(^7\) sparks new efforts to better understand and treat AUDs.

**REFERENCES**