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# Alcohol Use Disorder and Mortality Across the Lifespan:

## A Longitudinal Cohort and Co-relative Analysis

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## Abstract

**IMPORTANCE—**Excess alcohol consumption and alcohol use disorders (AUDs) are associated with substantially increased mortality. Efforts to reduce this toll require an understanding of their causes.

**OBJECTIVE—**To clarify the degree to which the excess mortality associated with AUDs arises (1) from the predispositions of the person who develops AUD (and which would likely be shared by close relatives) and (2) as a direct result of AUD itself.

**DESIGN, SETTING, AND PARTICIPANTS—**A prospective cohort and co-relative design study involving all individuals born in Sweden from 1940 to 1965 who had neither died nor migrated prior to 1973 or age 15 years (N = 2 821 036). They were followed up from January 1, 1973, until December 31, 2010. Alcohol use disorder was assessed from medical, criminal, and pharmacy registries. Half-siblings, full-siblings, and monozygotic twin pairs discordant for AUD were obtained from the Multi-Generation and Twin Register.

**MAIN OUTCOME AND MEASURE—**Death obtained from the Swedish Death registry.

**RESULTS—**Our cohort (1 447 887 males and 1 373 149 females) included 131 895 males and 42 163 females registered with AUD. The mean (SD) age at first AUD registration was 39 (13.4) years. We ascertained 127 347 and 76 325 deaths in the male and female subsamples, respectively.

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*Study concept and design:* Kendler, Ohlsson, K. Sundquist
*Acquisition, analysis, or interpretation of data:* All authors.
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Controlling for sex, educational status, and year of birth, the mortality hazard ratio associated with AUD was 5.83 (95% CI, 5.76–5.90) and varied—with an inverted *U*-shaped function—by age. Examining the AUD-mortality association in the general population and in relative pairs discordant for AUD exposure demonstrated substantial familial confounding in early to mid-adulthood: the AUD-associated mortality hazard ratio was much lower in discordant close relatives than in the general population. In middle to late adulthood, evidence for familial confounding decreased with increasing evidence for a direct effect of AUD on elevated mortality. In the oldest age group (65–70 years), the mortality hazard ratios were similar across the population and all relative pairs, suggesting that the excess mortality was largely a result of having AUD. Adding years since onset of AUD to the model showed that both increasing age and increasing years of duration of AUD contributed to the reduction of familial confounding in the association between AUD and elevated mortality.

**CONCLUSIONS AND RELEVANCE—**Excess mortality associated with AUD arises both from the predispositions of the person who develops AUD and the direct result of having AUD. The effect of predisposition is more prominent early in the life course and in the early years of AUD. The direct effect of AUD becomes progressively more important later in life and with longer duration of AUD. These results have implications for interventions seeking to reduce the elevated AUD-associated mortality.

> *Our intemperance it is, that pulls so many several incurable diseases upon our heads, that hastens old age, perverts our temperature [read as temperament], and brings upon us sudden death.* **Robert Burton, *The Anatomy of Melancholia (1660)*, 1926[1](p156)**

Excess alcohol consumption and alcohol use disorders (AUDs) are associated with substantially increased mortality.[2–7] In 2000, excessive alcohol use accounted for 85 000 deaths a year in the United States, representing the third leading modifiable cause of death.[8] Alcohol-related deaths contributed to the marked increase in all-cause mortality in US white non-Hispanic men from 1999 to 2013.[9] Efforts to reduce this toll require an understanding of its causes.

We sought to discriminate 2 mechanisms for this association. The increased mortality could arise from the habits and predispositions of the person who develops AUD or it could be a direct effect of AUD itself (eg, high alcohol consumption, withdrawal symptoms, frequent drunkenness, dietary deficiencies, and social isolation). While prevention methods focused on reducing alcohol consumption should affect excess mortality arising from the second mechanism, such approaches should not alter excess mortality resulting from the first mechanism.

Because human longevity is substantially heritable,[10–12] a co-relative design should help distinguish these 2 mechanisms. Excess AUD mortality due to this first mechanism should result in substantial familial confounding because unaffected close relatives of individuals with AUD, given the strong evidence of familial/genetic influences on most aspects of human behavior,[13] would often share their habits and predispositions. Under this scenario, the association between AUD and mortality should be much stronger in the general population than in close relatives discordant for AUD. By contrast, the second mechanism

would predict little familial confounding of the AUD-associated excess mortality as unaffected relatives would not be exposed to the direct effects of having AUD. Therefore, the increased mortality rate associated with AUD would be similar in the general population and in close relatives discordant for AUD.

However, clarifying the sources of the elevated mortality in AUD must also take into account changes in the magnitude of this excess by age and years of AUD.[2,3,14–16] Because we cannot assume that the underlying mechanism will be constant across the lifespan, the ideal study would have sufficient sample size to clarify patterns of familial confounding across the lifespan. We describe such a study based on a Swedish national sample with AUD ascertained from medical, criminal, and pharmacy registries.

## Methods

We collected information on individuals from Swedish population-based registers with national coverage. Registers were linked using each person's unique identification number. To preserve confidentiality, this number was replaced by a serial number. The study was approved by the Regional Ethical Review Board of Lund University; consent was not obtained as the study was based on registry information. For our definition of AUD, see the eAppendix in the Supplement. Year of death was assessed from the Swedish Mortality Register, containing causes of death from 1961 to 2010.

### Sample

The database began with all individuals born in Sweden from 1940 to 1965 who had neither died nor migrated prior to 1973 or age 15 years (N = 2 821 036). For this population, we included year of their first AUD registration, year of death, and year of emigration. We also included highest level (lifetime) of educational status (≤9 years, 10–11 years, and ≥12 years), sex, and year of birth.

### Statistical Analysis

In the first analysis, we used Cox proportional hazards models to investigate the risk for death from age 15 years until death (7.2%), emigration (4.6%), or follow-up until 2010 (88.2%) in individuals as a function of their first AUD registration. As the first registration for AUD could occur at varying ages, we treated AUD as a time-dependent covariate[17]: ie, from age 15 years until year of the first AUD registration, individuals were treated as AUD free, while from that AUD registration, they were considered registered for AUD. In the model, the proportionality assumption—that the hazard ratios (HRs) were constant over time—was not fulfilled because the AUD-mortality association varied across ages. Therefore, we allowed the effect of AUD to differ based on age intervals. We tested several different models and selected our model based on fit values (lowest Akaike Information Criterion [AIC][18]) and nonoverlapping 95% CIs for the effect of AUD. In the final model, we included the following age intervals: 15 to 24, 25 to 29, 30 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, and 65 to 70 years. Robust SEs were used to adjust confidence intervals to reflect individuals coming from the same family. We also included year of birth, education, and sex in the model.

We assessed the degree to which the results from the regression model reflected familial confounding using a co-relative design. With the Swedish Multi-Generation Register and the Swedish Twin Register, we identified all monozygotic (MZ) twin pairs and full- and half-sibling pairs. Using stratified Cox proportional hazards models, we refit all analyses within strata of specific relative set(MZ twins: 5507 total pairs, with 532 AUD discordant; full-siblings: 781 608 sibships, with 100 128 containing members discordant for AUD; and half-siblings: 291 520 total pairs, with 54 416 AUD discordant). Only sets where members differed in exposure to AUD at some age contributed to regression results. Within each strata, the HR was then adjusted for the familial cluster, and, therefore, accounts for an array of unmeasured genetic and environmental factors shared by relatives.

In the next step, we combined all 4 samples (ie, population, twin, full-siblings, and half-siblings) into 1 data set. From the population sample, we randomly selected the same number of individuals contained in the full-sibling analysis (n = 2 001 950). We performed 2 analyses. The first allowed all parameters for each sample to be independent within the samples and age intervals. The second modeled only the genetic resemblance, given evidence that resemblance for longevity in Sweden results only from genetic factors.[19] Within each age interval, we assumed that this parameter reflected genetic resemblance for each sample: ie, 0 for the population, 0.25 for the half-sibling, 0.5 for the full-sibling, and 1.0 for the twin sample. We compared these models by AIC. If the second model fit better, we obtained an HR for the slope of the familial confounding within each age interval and an improved estimation of the association among all relatives, but especially MZ twins, where the data were sparsest. While this genetic slope (GS) is estimated using information from the general population and all the relative pairs, it can most easily be understood from the following formula: HR_MZd = HR_GP × GS. That is, the estimated HR from discordant MZ twins (MZd) is obtained by multiplying the HR estimated from the general population (GP) by GS. Thus, a GS near unity means that the HRs are similar in the population and discordant MZ twin pairs, suggesting little familial confounding and a potential causal association between AUD and mortality. AGS value approaching zero means a sharp decline in the HRs across relative pairs of increasing affinity and, therefore, reflects a high degree of familial confounding.

In a final step, we investigated whether the familial confounding was mainly a result of age vs time since first AUD registration. Using the combined data set, we constructed 4 new parameters for years since first AUD registration: 1 to 5, 6 to 10, 11 to 20, and 21 or more years. Using the same modeling framework, we first fitted a stratified Cox regression model allowing these 4 parameters to be independent within each sample and age interval. We then obtained a slope for the familial confounding for each of the 4 parameters, which describe years since registration and within each age interval. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc).[20]

## Results

### Descriptive Findings

Key descriptive features of our cohort are depicted in the Table. Alcohol use disorder registration was associated with a substantially elevated mortality rate, with the mortality

HR (mHR) controlling for sex, educational status, and year of birth estimated at 5.83 (95% CI, 5.76–5.90). However, the mHR was not constant over time, with a linear model suggesting a rapid decline with increasing age (age by AUD HR, 0.64; 95% CI, 0.64–0.65). Therefore, we examined the effect of AUD on mortality in our entire population as a function of age. As seen in Figure 1, the AUD-associated mHR began at 5.04 (95% CI, 4.38–5.79) in the youngest age group(15–24 years), increased with age reaching a maximum at ages 30 to 39 years (8.19; 95% CI, 7.90–8.50), and then began a slow monotonic decline until ages 65 to 70 years (4.14; 95% CI, 3.96–4.33).

## Co-relative Analyses

We next examined the association between AUD and mortality by age group in the general population and in half-siblings, full-siblings, and MZ twin pairs discordant for AUD. Our model, which predicted the mHR as a function of degree of genetic association among the relative pairs, fit the data well (AIC of model vs raw data: 4 090 815.9 vs 4 090 817.2). Parameter estimates are seen in Figure 2. In early adulthood, the mHR in close relatives discordant for AUD exposure was much lower than that seen in the general population. In particular, the estimated mHR conditional on AUD in discordant MZ twins did not differ significantly from 1 for ages 15 to 24 years and 25 to 29 years. By age 40 years, the estimated mHRs for the general population and for discordant close relative pairs were less discrepant. In MZ pairs, the mHR in the twin with AUD was more than 4 times greater than the unaffected twin. However, the mHR in discordant MZ twins was still much less than the mHR of nearly 8 seen in the general population. Finally, above the age of 55 years, the differences in mHR between the population and relatives declined further so that by our last age period (65–70 years), no appreciable differences were seen in the mHR across all our groups with all values around 4.

These analyses did not control for years of AUD exposure. To investigate this question, our next model examined both age and years since first AUD registration divided into 4 periods. Our model again fit the data well (AIC of model vs raw data: 4 002 503.9 vs 4 002 519.9). The estimated parameters from this model illustrated 2 major trends (Figure 3). First, aside from the anomalous results (likely due to small sample sizes) for ages 65 to 70 years within 1 to 5 years of first registration, we saw the general trend observed in Figure 2: the slopes of the mHRs in the general population and increasingly close relatives were steeper at younger ages and gradually approached horizontal at older ages. Second, from age 40 years onward, within age periods, the differences in mHR across groups tended to decline with increasing years from first registration. However, this trend was less consistent in the oldest groups. We illustrate these trends in Figure 4, which depicts the GS of the mHRs across the 4 groups (general population and discordant half-siblings, full-siblings, and MZ twins) as a function of years since first AUD registration and age.

Although many of these estimates are not known with high precision, the general trends are clear. For individuals within 1 to 5 or 6 to 10 years of their first AUD registration, a strong monotonic trend was seen for slopes to increase (that is, demonstrate less confounding) with increasing age. For those 11 or more years past first registration, this trend was largely restricted to the youngest available age group (those 25–29 years for 11–20 years after onset

and 30–39 years for those ≥21 years past onset). Finally, within age groups, a general trend was seen for the values of the slopes to increase with increasing years since first AUD registration.

## Discussion

From ages 15 to 70 years, AUD was associated with a nearly 6-fold increase in all-cause mortality. This association is consistent with prior studies,[4,15,16,21] although considerably stronger than that estimated from 2 recent meta-analyses: 3.38 (95% CI, 2.98–3.84) in men, 4.57 (95% CI, 3.86–5.42) in women,[3] and 3.45 (95% CI, 2.96–4.02) in both sexes.[2] Congruent with prior findings,[3,14] the magnitude of this association varied substantially by age, being weakest in late adulthood.

Our major goal was to elucidate the mechanisms of the AUD-mortality association. To what degree does the excess rate of death in individuals with AUD arise because of predispositions in the person who develops AUD vs results from the direct effect of the AUD itself?

We first addressed this question by examining the pattern of mHRs in 9 age groups in unrelated members of the general population and in half-siblings, full-siblings, and MZ twins discordant for AUD. In the younger age groups (ie, those <40 years), mHRs (1)were much greater in the general population than in the discordant relative pairs, (2) became progressively smaller in more closely related individuals, and (3) did not differ from unity in discordant MZ twins. This is the pattern expected for strong familial confounding. That is, the association between AUD and excess mortality in these age groups would appear to result largely from shared familial factors rather than the direct effects of AUD itself. These factors might include personality traits, such as impulsivity or novelty seeking, or a proclivity toward other substance use or misuse, which are both associated with AUD[22,23] and under genetic influence.[24,25]

By middle adulthood (ages 40–59 years), the picture shifts. The mHRs in close relatives were much lower than in the general population but now also substantially greater than unity. This is the picture that would be expected if the AUD-mortality association arose from a mixture of familial confounding and direct causal relationships. Direct causal effects of AUD are likely to be complex and include exposure to high levels of alcohol intake often over long periods, frequent intoxication, and the associated poor judgment in dangerous situations (eg, driving and physical aggression), poor nutrition, increased tobacco and other drug use, social isolation, and poorer health care. Of course, for some of these associations (eg, AUD and social isolation or drug use), causal effects are likely to be bidirectional. Finally, by late adulthood, little difference was seen in the mHRs across the general population and all our samples of discordant relatives including discordant MZ twin pairs. This is the picture expected if the preponderance of the AUD-mortality association arose as a direct result of the AUD itself.

The findings from our co-relative design suggesting a direct causal effect of AUD on mortality is consistent with several prior lines of evidence. First, naturalistic studies show

declines in mortality with reduced alcohol consumption at a population level (eg, Prohibition in the United States[26] and the Gorbachev reforms in the Soviet Union[27]). Second, a previous meta-analysis showed that alcohol-dependent individuals who continued to drink heavily had significantly greater mortality than alcohol-dependent individuals who reduced their alcohol intake.[2] Third, 6 randomized clinical trials have shown that interventions leading to reduced drinking also reduced mortality rates.[28]

Our final analyses added to our initial model years since first AUD registration, with the goal of clarifying the degree to which chronological age or years of AUD were most predictive of the level of familial confounding in the AUD-mortality association. The results suggested that both contributed. That is, the older the individual and the longer they had AUD, the larger the proportion of the AUD-mortality association that appeared to be causal.

These results should be interpreted in the context of 6 potential methodological limitations. First, we detected individuals with AUD from official registry records obviating the need for cooperation or accurate recall. The validity of our method is supported by high concordance for registration across our modes of ascertainment.[29] However, prevalence of AUD in this sample was substantially lower than estimated from interview surveys in the United States[30,31] and Norway.[30,32] Therefore, our AUD cases are likely to be more severely affected than those ascertained from population-based interview studies. The stronger association with mortality for AUD observed in this vs prior samples[2,3] might result from the high average severity of our ascertained cases and, in particular, our use of medical registry, as among individuals with AUD in the general population, treatment is associated with increased mortality.[2]

Second, our sample likely contained heavy-drinking individuals never registered for AUD. To explore how much this might bias our results, we examined alcohol consumption at ages 18 to 20 years available from 2 years of military conscription records (1969–1970) in male-male sibling pairs discordant for lifetime AUD registration.[33] Standardized alcohol consumption scores for those who did and did not have a subsequent AUD registration were +0.40 and −0.04, respectively. The unaffected sibling from discordant pairs had a mean consumption score of +0.01, suggesting only modestly increased drinking at least in late adolescence. Nonetheless, some of the familial confounding observed in our study could arise because nonregistered close relatives of AUD probands drink at higher rates than the general population.

Third, our models included both men and women with sex as a covariate, thereby controlling for the stronger AUD-mortality association in females observed in both our and prior samples.[15,21] The substantially lower prevalence of AUD in women in our sample made it impossible to informatively fit more complex models to the sexes separately.

Fourth, our integrative model assumed that familial confounding of the AUD-mortality association was mediated genetically. The validity of this assumption was supported by the good fit of these models. We directly evaluated this assumption by comparing the AUD-mortality association in half-siblings reared together or apart. Consistent with our

assumption, we found no evidence for differences in the degree of confounding, despite differences in shared environmental exposures in the half-sibling groups.

Fifth, results from our younger age groups, in which individuals could be included only if they were born in the earlier years of our cohort and had an early age at first registration, could be biased. We repeated analyses for a cohort born from 1966 to 1990 for which we could define 4 age groups: 15 to 24, 25 to 29, 30 to 39, and 40 to 44 years. Although estimates for the oldest group were very imprecise, we replicated our key finding of decreasing level of confounding of the AUD-mortality association with increasing age (eFigure in the Supplement).

Finally, the Swedish mortality registry contains *International Classification of Diseases* codes for cause of death. An important future research question would be the degree to which an examination of these codes can shed further light on the causal association between AUD and premature mortality.[34]

## Conclusions

Using a large-scale population-based prospective cohort design, we found a substantial increase in mortality in both men and women registered with AUD. Using a co-relative design, we showed that this excess mortality appears to arise both from the predispositions of the person who develops AUD and from the direct result of the AUD itself. The effects of the predispositions were more prominent early in the life course and in the earlier years of AUD. The direct effect of AUD on mortality became progressively more important later in life and later in the course of AUD. These results have clear implications for interventions that seek to reduce the substantially elevated rates of mortality in those with AUD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Key Points

**Question**

What causes the substantial excess mortality associated with alcohol use disorders (AUDs)?

**Findings**

In this cohort and co-relative study in Sweden, AUD was associated with excess mortality. In pairs of relatives discordant for AUD, substantial familial confounding was seen for the AUD-mortality association in early to mid-adulthood, with the degree of confounding decreasing strongly with age.

**Meaning**

Excess mortality associated with AUD arises both from the predispositions of the person who develops AUD and the direct result of having AUD, and the effect of predisposition is more prominent early in the life course and in the early years of AUD.

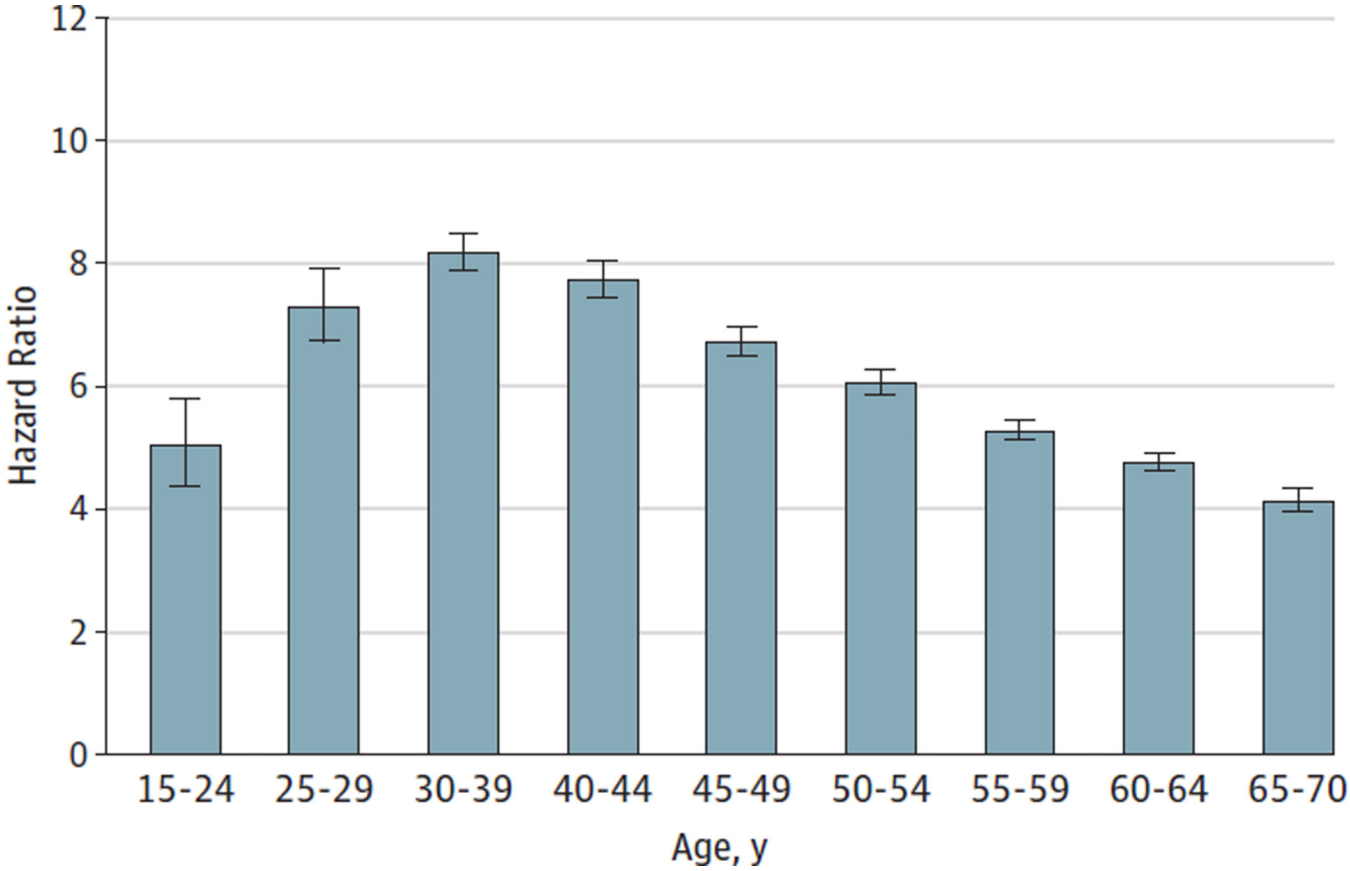


**Figure 1. Observed Hazard Ratio in the General Population for Death as the Outcome With Alcohol Use Disorder Registration as a Time-Dependent Coefficient as a Function of Age**

Sex, educational status, and year of birth are included in the model as covariates.

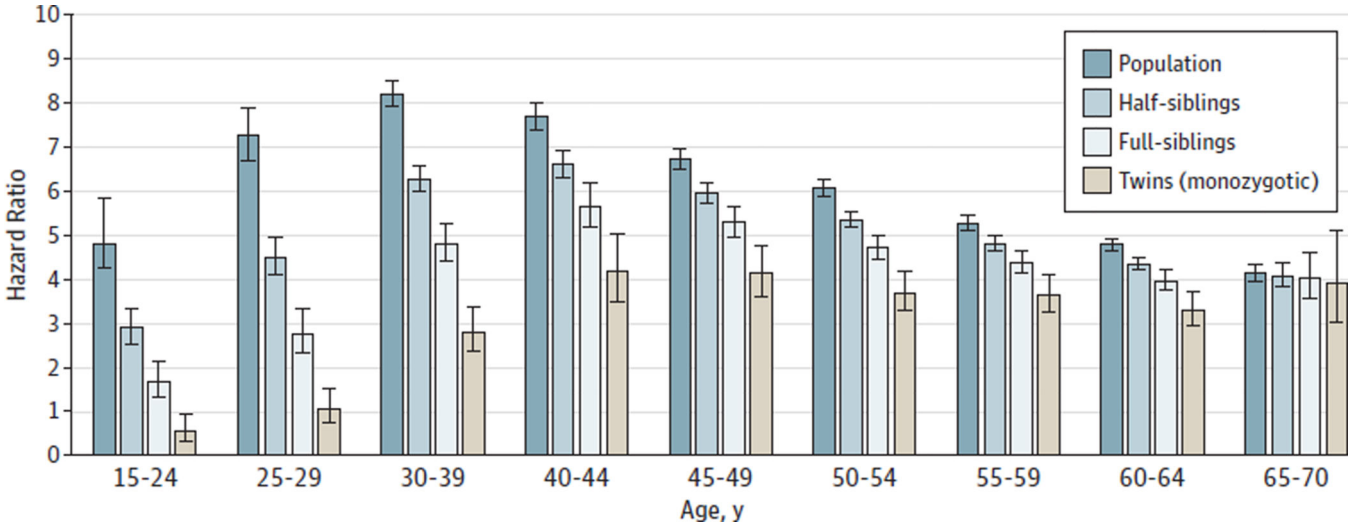


**Figure 2. Expected Hazard Ratio for Death as the Outcome With Alcohol Use Disorder Registration as a Time-Dependent Coefficient as a Function of Age in 9 Age Groups From Late Adolescence to Late Adulthood**

Sex, educational status, and year of birth are included in the model as covariates. Estimated hazard ratios are presented for the general population and in half-siblings, full-siblings, and monozygotic twins discordant for alcohol use disorder.

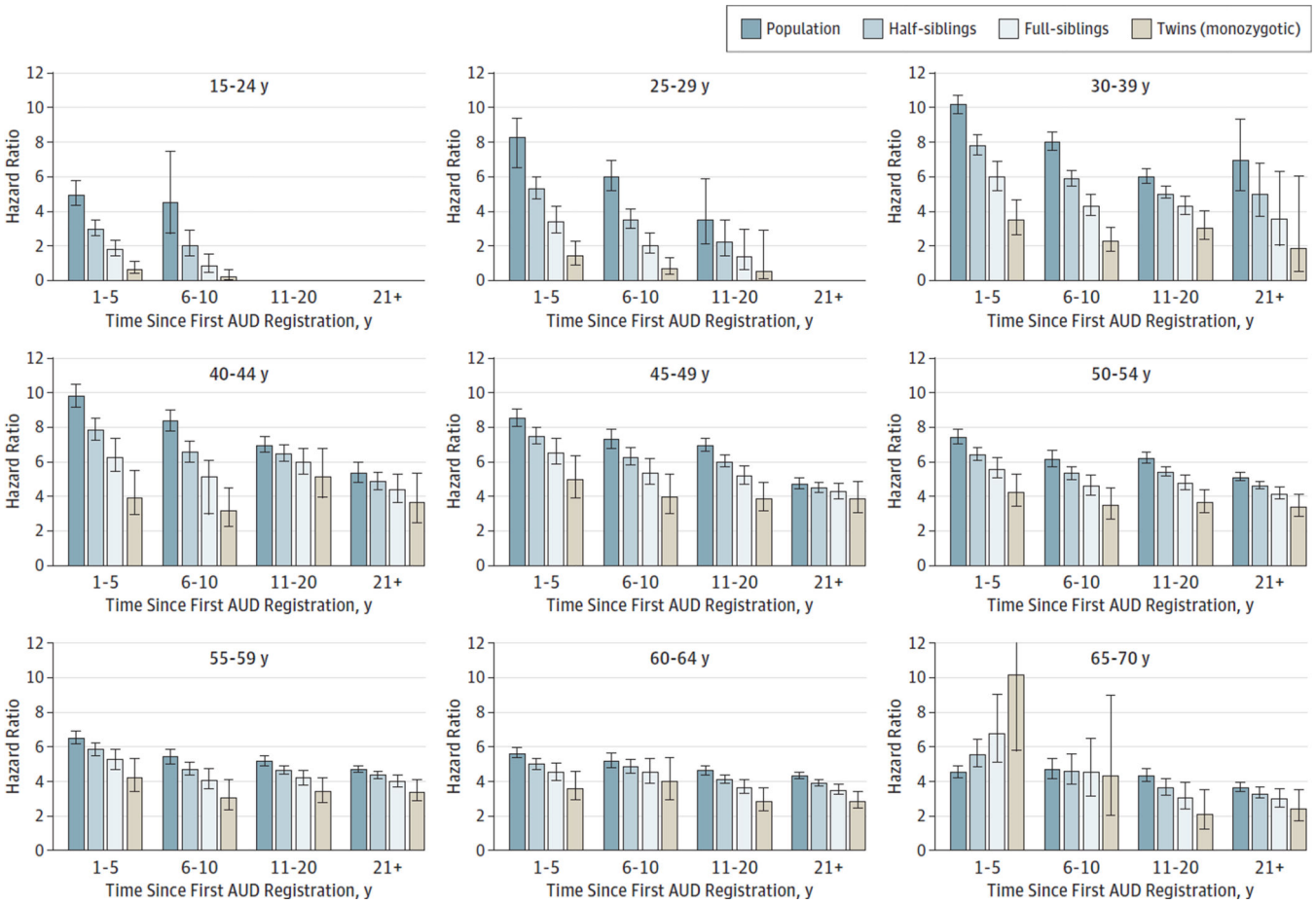


**Figure 3. Hazard Ratio for Death as the Outcome With Alcohol Use Disorder (AUD) Registration as a Time-Dependent Coefficient as a Function of Age From Late Adolescence to Late Adulthood and Within Each Age Group as a Function of Years Since First AUD Registration**

Sex, educational status, and year of birth are included in the model as covariates. Estimated hazard ratios are presented for the general population and in half-siblings, full-siblings, and monozygotic twins discordant for AUD.

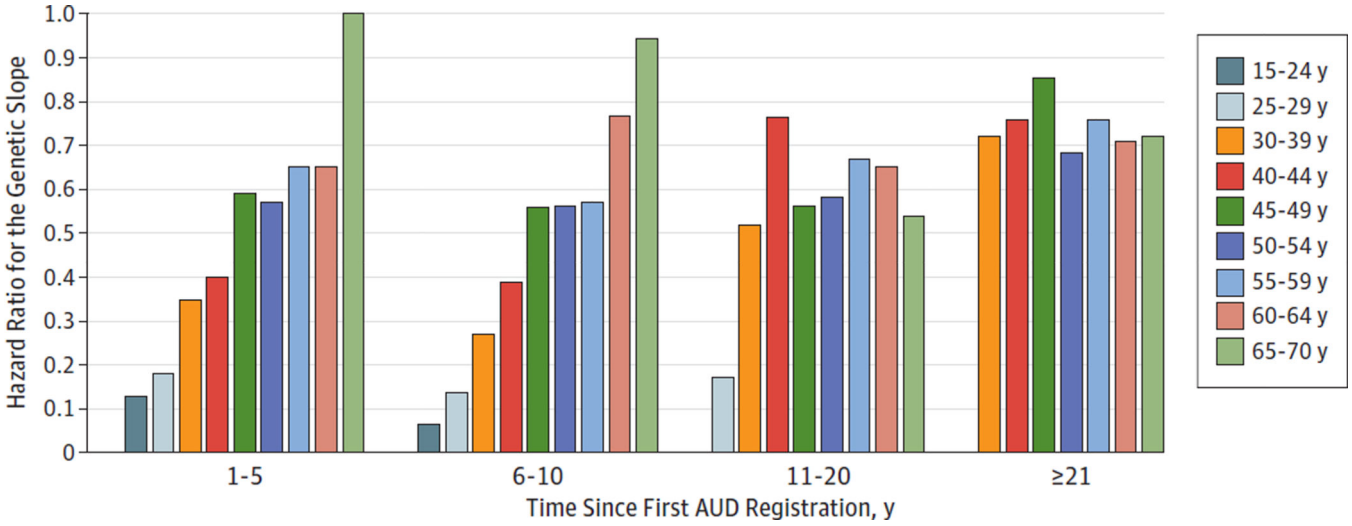


**Figure 4. Evidence for Familial Confounding of the Alcohol Use Disorder (AUD)–Mortality Association as a Function Both of Age and Time Since First AUD Registration**

The figure depicts the hazard ratio for the genetic slope in the general population and pairs of discordant half-siblings, full-siblings, and monozygotic twins. The lower the value for the slope, the more evidence there is for familial confounding. A slope of unity indicates no confounding consistent with the hypothesis that all the effect of AUD on mortality is causal.

## Table

Descriptive Statistics Individuals Born in Sweden From 1950 to 1965 Alive at Age 15 Years or in 1973 With AUD Registration Measured From 1973 Onward

| Characteristic | No. (%) |
|---|---|
| Sample size | 2 821 036 |
| AUD registration | 174 058 (6.17) |
| Age at first AUD registration, mean (SD), y | 39.0 (13.4) |
| Percentile | |
| 25th | 28 |
| 50th | 38 |
| 75th | 49 |
| Dead | |
| AUD | 44 035 (25.3) |
| No AUD | 172 067 (6.5) |
| Mean age at death, y | |
| AUD | 50.8 |
| No AUD | 49.8 |
| Follow-up time, mean (SD), y | 41.9 (9.2) |

Abbreviation: AUD, alcohol use disorder.