Data Supplement for Edwards et al., Alcohol Use Disorder and Risk of Suicide in a Swedish Population-Based Cohort. Am J Psychiatry (doi: 10.1176/appi.ajp.2019.19070673)

Supplementary Material

The following ICD codes were used to identify psychiatric and substance use disorders:

Suicide
As noted in the primary text, codes corresponding to both known suicides and death of undetermined intent were included. Distinctions between completions and attempts, where necessary, were determined using the Cause of Death Register.
ICD-8 codes E950-E959, E980-987
ICD-9 codes E950-E959, E980-987
ICD-10 codes X60-X84, Y10-Y34

Alcohol Use Disorder
ICD-8 codes 291, 303, 205A, 357F, 425F, 535D, 571A-D, 980, V79B;
ICD-9 codes 291, 303, 305A, 357F, 425F, 535D, 571A-D, 980, V79B;
ICD-10 codes F10 (excluding F10.0), Z50.2, Z71.4, E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K70.0-K70.9, K85.2, K86.0, O35.4, T51.0-T51.9

Drug Abuse
ICD-8 codes 304;
ICD-9 codes 292, 304, 305 (excluding 305.0);
ICD-10 codes F10-F19 (excluding F10 and F17)

Affective Disorders
ICD-8 codes 296.1, 296.0, 296.2-8,300.4;
ICD-9 codes 296A, 296B-296E, 296W, 300E, 311;
ICD-10 codes F30-F39 except 32.3

Psychotic Disorders
ICD-8 codes 291, 295, 296.99, 297, 298, 299;
ICD-9 codes 291-292, 295, 296X, 297, 298, 299;
ICD 10 codes F20-F25, F28-F29, F32.3, x.5 in F10-F19

Personality Disorders
ICD-8 code 301;
ICD-9 code 301;
ICD-10 code F60

Phobia and Anxiety Disorders
ICD-8 codes 300.00, 300.20;
ICD-9 codes 300A, 300C;
ICD-10 codes F40-41

Other Psychiatric Disorders
ICD-8 codes 300.1, 300.5, 300.6, 300.7, 300.88, 300.99;
ICD-9 codes 300B, 300F, 300G, 300H, 300W, 300X, 307B, 307F;
ICD-10 codes F43 -F45, F48, F50

Cases of alcohol use disorder were also identified from the Suspicion and Crime Registers, for individuals who had at least two convictions of drunk driving (law 1951:649) or drunk in charge of maritime vessel (law 1994:1009). The Prescribed Drug Register was also used, identifying those with a prescription for disulfiram (N07BB01), acamprosate (N07BB03), or naltrexone (N07BB04).

Cases of drug abuse were also identified from the Suspicion Register by codes 3070, 5010, 5011, and 5012; from the Crime Register by references to laws covering narcotics (law 1968:64, paragraph 1, point 6) and drug-related driving offences (law 1951:649, paragraph 4, Subsection 2 and paragraph 4A, Subsection 2); and in the Prescribed Drug Register in individuals (excluding those suffering from cancer) who had retrieved (in average) more than four defined daily doses a day for 12 months from either of Hypnotics and Sedatives (Anatomical Therapeutic Chemical (ATC) Classification System N05C and N05BA) or Opioids (ATC: N02A).

Supplemental Co-Relative Model

We lacked the statistical power to include monozygotic (MZ) twin pairs in the co-relative analyses described in the primary text. Accordingly, we conducted a complementary analysis in which the logarithm of the hazard ratios is assumed to be a linear function of the genetic correlation between different relative pairs – i.e., rG=0.125 for cousins, 0.25 for half-siblings, 0.5 for siblings, and 1.0 for monozygotic twins – and of AUD. In this model, the estimated risk for the affected member of a discordant MZ twin pair is extrapolated based on the estimates for other co-relative pairs. This model includes and interaction term between AUD and genetic resemblance and enables us to derive HRs for each relative group including MZ pairs. We compare the model fit, operationalized by Akaike's Information Criterion value, from this model to a model based on that presented in the primary text, where HRs are estimated independently for each co-relative group and the general population. We note that the "primary" model here, in

contrast to that presented in the main text, presents hazard ratios averaged across observation time in order to facilitate direct comparison to the supplementary, extrapolated estimates.

As noted in the main text, half-siblings have an elevated risk of AUD and SU, potentially due to factors related to disrupted family structure that are influenced by genetic and/or environmental factors. We hypothesized that the inclusion of half-siblings in our model would likely result in deviation from the linear assumption described above. We therefore also tested an exploratory model in which half-siblings were excluded. Only models unadjusted for covariates were tested, with the primary goal of extrapolation of the MZ estimate, which, contingent on model fit, could be compared to the other co-relative-based estimates depicted in Figure 1 and Table 3 of the primary text. An AIC for this supplementary model comparable or superior to that of the primary model would indicate that we can be confident in the extrapolated estimate for SU risk for the AUD-affected member of a MZ twin pair. A substantial detriment in fit would suggest that such an extrapolation would be inappropriate.

Results are presented in **Table S4**. The best model fit was for the supplemental model excluding half-siblings (AIC=444480.04), which represented a substantial improvement over the primary model (i.e., one parallel to that presented in the primary text, but excluding half-siblings). When half-siblings are included, the fit was quite similar regardless of whether the hazard ratio was assumed to be a function of AUD and genetic correlation between pairs, with a slight advantage for the model presented in the primary text. Notably, the extrapolated MZ pair estimate was nearly identical regardless of whether half-siblings were included in the model: HR=3.67-3.69, consistent with the finding reported in the primary text that HRs decreased within co-relative pairs as degree of genetic relatedness increased.

MZ twins represent the most complete “control” available in observational epidemiological studies with respect to genetic liability, which otherwise represents a potential confounding factor when examining the association between two outcomes. Thus, these estimates provide additional support for two findings detailed in the primary text, namely: i)

shared genetic liability contributes to the association between AUD and SU, as evidenced by the continued decrease in HR as increasing degrees of relatedness are accounted for; and ii) a substantial, and likely causal, residual association remains for AUD and SU, as evidenced by the difference between the MZ-based HR (~3.7) and 1, the latter of which would be expected were the association due entirely to genetic confounding.

Deaths of Undetermined Intent

As demonstrated in **Table S5** and noted in the primary text, HRs associated with AUD were reduced when deaths of undetermined intent (UDI deaths) were excluded from suicide cases. Of N=15,528 suicide cases, N=3,933 (25.3%) were classified as UDI deaths. Among suicide cases with an AUD registration (N=4,387), UDI deaths were more common, accounting for N=2135 (48.7%) of cases (χ^2_1=1760.86, p<0.0001).

Among AUD cases registered for suicide, we examined differences across UDI status. Age of AUD onset was lower for those death was classified as of UDI (mean age [SD] = 30.02 [8.41] vs. 33.46 [10.20]; t(4302.2) = 12.13, p<0.0001), as was age at death (mean age [SD] = 36.79 [10.42] vs. 41.46 [9.81], t(4329.1) = 15.28, p<0.0001). For those with UDI deaths, less time elapsed between the first AUD registration and death (mean [SD] years = 6.77 [7.83] vs. 8.01 [7.84], t(4385) = 5.22, p<0.0001). Most psychiatric diagnoses were less common among those with UDI deaths, including affective disorders (χ^2_1=242.63, p<0.0001), psychotic disorders (χ^2_1=106.68, p<0.0001), personality disorders (χ^2_1=18.35, p<0.0001), phobias/anxiety disorders (χ^2_1=38.16, p<0.0001), and other grouped psychiatric disorders (χ^2_1=55.77). Only a history of drug abuse was *more* common among those whose death was classified as of UDI (χ^2_1=30.15, p<0.0001).

These findings raise the possibility that, in the absence of a history of other psychiatric disorders, coroners/medical examiners may be less able or inclined to confidently classify a death as a suicide. The younger age at AUD onset, younger age at death, and higher

prevalence of DA among those whose deaths were classified as of UDI further indicates that these individuals exhibited relatively high levels of externalizing behavior – for example, earlier age of AUD onset is typically considered to be a feature of an externalizing/impulsivity-driven AUD typology[1,2]. Such individuals may engage in reckless and potentially lethal behavior without suicidal intent[3,4], thus complicating their posthumous classification.

Severity of AUD

We considered the possibility that suicide risk may vary as a function of AUD severity. AUD cases identified using registry data are generally considered to be more severely affected than cases ascertained via other methods (e.g., self-report). Recurrence is one index of severity, but in the context of survival models wherein suicide is the outcome of interest, recurrence would potentially provide a misleading picture: Individuals who died by suicide between their first and second registrations – potentially those most severely affected by AUD – would be censored. Given the data available to us, we determined that the most appropriate approach would be to examine whether suicide risk differed as a function of self-reported alcohol consumption, which is correlated with AUD risk. This data is available for a cohort of N=44,894 Swedish men born in 1951, who responded to questions about alcohol consumption as part of the Military Conscription Registry.

Drinking behavior was assessed as an alcohol score, which was constructed after a factor analysis based on the following questions: “How often do you drink medium/strong beer?”, “How much do you drink when you drink medium/strong beer?”, “How often do you drink wine/strong wine?”, “How much do you drink when you drink wine?”, “How much do you drink when you drink liquor?”, “How often do you drink so that you feel drunk?”, “Do you often get a hangover?” and “Have you ever been arrested for drunkenness?” We used these items to construct an Alcohol Score, which was divided into 3 groups: low use/misuse (0-25th percentile), middle use/misuse (26-75 percentile) and high use/misuse (76-100 percentile).

Replicating our primary analyses, but using the Alcohol Score as a predictor rather than AUD, yielded the following results, where a low use/misuse score is the reference category: middle use/misuse HR=1.03 (0.83, 1.28); high use/misuse HR=1.82 (1.45, 2.27). These results should be considered with caution, as they are based on a small sample of men in a limited birth cohort.

TABLE S1. Polychoric correlations between psychiatric predictors/covariates.
Correlations are provided for each pair of variables. All asymptotic standard errors were <0.01.

	Alcohol Use Disorder	Drug Abuse	Affective Disorders	Psychotic Disorders	Personality Disorders	Phobia/ Anxiety Disorders
Drug Abuse	0.72	1				
Affective Disorders	0.49	0.52	1			
Psychotic Disorders	0.87	0.81	0.63	1		
Personality Disorders	0.54	0.62	0.64	0.67	1	
Phobia/Anxiety Disorders	0.49	0.54	0.72	0.57	0.62	1
Other Psychiatric Disorders	0.42	0.48	0.69	0.51	0.57	0.79

TABLE S2. Hazard ratios (HR) and 95% confidence intervals (CI) for models in which a single psychiatric predictor (AUD, psychotic disorders, etc.) of death by suicide was included. Birth year and parental education were included as covariates; the psychiatric predictor was coded as time-dependent.

Months of Observation	**0-59**		**60-119**		**120-179**		**180-239**		**240-299**		**300+**	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Women												
AUD	170.4	109.2, 266.1	58.6	42.5, 80.7	55.4	42.8, 71.7	34.8	26.7, 45.3	42.3	33.2, 53.9	25.7	22.5, 29.3
Other Psychiatric Disorders	-[1]	-	34.0	1.61, 72.0	39.2	25.3, 60.7	22.0	14.6, 33.0	18.8	14.2, 24.7	17.1	15.2, 19.3
Phobia and Anxiety Disorders	-	-	-	-	37.8	21.3, 67.0	21.1	13.6, 32.8	19.5	14.8, 25.7	18.9	16.8, 21.2
Personality Disorders	20.7	6.56, 65.3	48.0	35.4, 65.1	36.8	28.5, 47.6	35.4	28.0, 44.8	29.1	23.3, 36.5	23.5	20.7, 26.7
Psychotic Disorders	68.2	37.2, 125.2	76.1	59.8, 96.9	53.1	43.1, 65.3	46.3	38.2, 56.1	33.5	27.8, 40.3	32.8	29.6, 36.3
Affective Disorders	71.1	26.6, 189.8	75.2	53.9, 105.0	48.6	37.6, 62.8	51.6	42.0, 63.4	30.6	25.3, 37.2	24.2	21.9, 26.9
Drug Abuse	66.9	31.4, 142.9	53.3	38.3, 74.0	47.7	36.7, 62.0	37.7	29.4, 48.4	33.9	27.1, 42.4	39.2	25.1, 43.7
Men												
AUD	38.4	27.2, 54.1	23.6	20.3, 27.6	22.2	19.7, 25.0	20.6	18.4, 23.0	19.3	17.3, 21.5	11.8	11.1, 12.7
Other Psychiatric Disorders	-	-	6.96	0.98, 49.3	9.84	4.09, 23.6	15.2	10.1, 22.7	14.7	11.6, 18.7	12.0	10.9, 13.2
Phobia and Anxiety Disorders	-	-	14.5	3.65, 58.1	24.3	14.8, 39.8	18.4	13.3, 25.3	14.6	11.8, 18.1	11.3	10.3, 12.4
Personality Disorders	9.83	3.68, 26.3	21.9	17.3, 27.7	18.8	15.6, 22.6	17.7	14.9, 20.9	14.6	12.4, 17.3	11.3	10.2, 12.6

Psychotic Disorders	39.2	24.4, 62.9	35.5	30.1, 41.9	28.8	25.3, 32.8	23.0	20.4, 26.0	20.2	18.0, 22.6	15.7	14.7, 16.8
Affective Disorders	29.3	9.4, 91.6	27.9	19.9, 39.1	29.9	24.3, 36.7	24.9	21.0, 29.4	20.2	17.5, 23.3	16.2	15.1, 17.4
Drug Abuse	28.0	14.4, 54.4	31.0	25.8, 37.3	25.5	22.1, 29.4	25.6	22.5, 29.0	21.8	19.3, 24.6	14.0	13.0, 15.1

[1] In some cases, data were too sparse to produce hazard ratio estimates for specific predictors.

TABLE S3. Hazard ratios (HR) and 95% confidence intervals (CI) for suicide as a function of AUD age of onset (in years), which was categorized as <25, 25-35, 35-45, 45-55, and >55. Unadjusted models included only birth year and mean parental education as covariates; adjusted models accounted for time-dependent psychiatric comorbidity as well. Hazard ratios are averaged across observation time.

	Women				**Men**			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
Age	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<25 (reference)	1	n/a	1	n/a	1	n/a	1	n/a
25 to <35	1.22	1.06-1.40	0.70	0.60-0.83	1.03	0.96-1.11	0.79	0.73-0.86
35 to <45	1.11	0.96-1.29	0.46	0.39-0.55	0.84	0.77-0.91	0.57	0.52-0.62
45 to <55	0.87	0.72-1.05	0.40	0.32-0.49	0.58	0.51-0.65	0.42	0.37-0.47
55 or older	0.44	0.25-0.78	0.29	0.16-0.51	0.36	0.26-0.49	0.32	0.23-0.43

TABLE S4. Supplemental co-relative model results. Model fit (AIC) is included both for the supplemental model described above and for the model described in the primary text. The latter was run including half-siblings as in the primary text, and excluding half-siblings to facilitate direct comparisons to the supplemental models.

		Half Siblings Included		Half Siblings Excluded	
Sample	rG	HR	95% CI	HR	95% CI
Population	0	22.47	21.62, 23.35	22.46	21.62, 23.34
Cousins	0.125	17.93	17.14, 18.75	17.91	17.11, 8.75
Half Siblings	0.25	14.30	13.30, 15.37	n/a	n/a
Full Siblings	0.50	9.10	7.91, 0.48	9.08	7.86, 10.49
Monozygotic twins	1.00	3.69	2.77, 4.90	3.67	2.74, 4.91
AIC:					
Supplemental model		446145.92		444480.04	
Primary model		446137.75		446686.72	

rG=genetic correlation; HR=hazard ratio; CI=confidence interval; AIC=Akaike Information Criterion

TABLE S5. Adjusted hazard ratios (HR) (averaged across observation time) and 95% confidence intervals (CI) for alcohol use disorder and covariates predicting death by suicide among native Swedish women and men born between 1950 and 1970, excluding deaths of undetermined intent (N=3933).

	Women		Men	
	HR	95% CI	HR	95% CI
Alcohol Use Disorder	2.03	1.74, 2.38	2.02	1.81, 2.27
Drug Use Disorder	1.78	1.52, 2.08	1.71	1.54, 1.89
Affective Disorder	7.46	6.09, 9.14	5.10	4.58, 5.67
Psychotic Disorder	7.27	5.82, 9.08	5.12	4.50, 5.82
Personality Disorder	1.94	1.68, 2.25	1.55	1.39, 1.72
Phobia/Anxiety Disorder	1.09	0.92, 1.31	0.91	0.79, 1.06
Other Psychiatric Disorder	1.51	1.26, 1.80	1.36	1.17, 1.57
Birth Year	0.96	0.95, 0.97	0.98	0.97, 0.98
Mean Parental Education				
1 (reference)	n/a	n/a	n/a	n/a
1.5	0.96	0.86, 1.06	0.83	0.78, 0.89
2	1.16	1.05, 1.27	0.88	0.83, 0.94
2.5	1.02	0.88, 1.20	0.78	0.70, 0.86
3	1.21	1.05, 1.40	0.90	0.82, 0.99

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