Title: Risk of alcohol-related liver disease in the offspring of parents with alcohol-related liver disease: A nationwide cohort study

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Abstract

Background and aims: Offspring of patients with alcohol-related liver disease (ALD) may have higher risk of ALD. We examined their risk of ALD and survival with ALD.

Approach & Results: We used Danish nationwide registries to identify offspring of patients diagnosed with ALD in 1996–2018 and 20:1 matched comparators from the general population. They were followed for ALD diagnosis through 2018. We used landmark competing risk analysis to estimate the age-specific absolute and relative 10-year risks of ALD.

ALD was diagnosed in 385 of 60,707 offspring and 2,842 of 1,213,357 comparators during 0.7 and 14.0 million person-years of follow-up, respectively, yielding an incidence rate ratio of 2.73 (95% CI 2.44–3.03). The risk of being diagnosed with ALD within the next 10 years peaked at age 55 years for offspring and age 57 years for comparators with 10-year risks of 1.66% (95% CI 1.16–2.30) in offspring and 0.81% (95% CI 0.68–0.97) in comparators at these ages. Offspring were younger at ALD diagnosis than comparators (median age of 47.4 vs 48.9 years), yet slightly more of them had developed cirrhosis (60.3 % vs. 58.7%). Survival after ALD diagnosis was similar in offspring and comparators, adjusted hazard ratio = 1.03 (95% CI 0.88–1.21), so on average offspring died younger due to their younger age at diagnosis.

Conclusions: Offspring of patients with ALD had a low but increased risk of ALD. Screening offspring for chronic liver disease may be unnecessary, but other interventions to mitigate alcohol-related harm should be considered.

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Introduction

Alcohol-related liver disease (ALD) is a significant contributor to premature deaths worldwide, accounting for 22 million disability-adjusted life-years lost every year [1]. Many of those who are diagnosed with ALD have been drinking hazardously for decades, 20 years on average [2], so it is likely that their offspring have been exposed to parental alcohol abuse. These offspring are the subjects of this study.

Knowledge of these offspring's risk of ALD will guide decisions about screening for chronic liver disease or other interventions, e.g., screening for alcohol use disorder and broader social support [3]. Information on the expected ALD risk in the offspring is also valuable for clinical counseling of both parents and offspring. Previous studies have found an increased risk of alcohol use disorder in offspring of parents with hazardous alcohol consumption [4], but no previous study has examined whether the same is true for the harder clinical outcome of ALD.

Danish nationwide registries allow parent-child linkage since 1960, and hospital diagnoses of ALD have been recorded since 1977 [5,6]. We, therefore, examined the risk of ALD in offspring of individuals with ALD and matched comparators.

Methods

We identified offspring of patients diagnosed with ALD in 1996–2018 and comparators from the general population matched to them on age, sex, and birth year. We followed offspring and comparators through 2018 for diagnoses of ALD and estimated their absolute and relative risk of ALD. Finally, we compared survival after diagnosis of ALD between offspring and comparators.

Data sources

We used data from four Danish nationwide registries: The National Patient Registry [6], the Registry of Cause of Death [7], the Civil Registration System [5], and the Education Registry [8]. All the included data sources are described further in Supplementary Table S1. We used the educational attainment of the ALD parent as a proxy for socioeconomic status. Educational attainment may be less influenced by harmful alcohol consumption during adulthood than are other proxies of socioeconomic position such as employment status and income [9]. It was a limitation that we did not have data on the educational attainment of the offspring. However, an offspring's final educational attainment may not have been reached at the time of the parent's ALD diagnosis [10].

Virtually all healthcare in Denmark is provided by the national health authorities, allowing true population-based register-linkage studies covering all inhabitants of Denmark [5]. Data were linked by use of the personal identification number, a unique identifier assigned to all Danish inhabitants since 1968 [5]. All linkages and identification of comparators were performed within Statistics Denmark, a governmental institution that collects and processes information for administrative and scientific purposes.

Offspring of patients with ALD

We restricted the study period to when diagnoses were coded in accordance with the International Classification of Diseases, 10th revision (ICD-10), which began in 1994, to ensure homogeneity of coding practices [6]. We first identified patients diagnosed with ALD (ICD-10: K70.x) in the hospital (through the National Patient Registry) or as an underlying or contributory cause of death (through the Registry of Cause of Death) during the 1996 to 2018 period [6,7]. We then used the parent-child linkage in the Civil Registration System to identify offspring of patients diagnosed with ALD [5]. We included offspring born any time before their parent was diagnosed with ALD but

excluded those offspring who had already died or been diagnosed with ALD before that date. We did not include offspring born after their parent's ALD diagnosis (n = 910), nor did we have data on diagnoses given by general practitioners since this data is not available in Danish nationwide registries.

Comparators

We identified twenty comparators for each offspring of patients diagnosed with ALD among the general Danish population. Matching took place on the index date (the date of the parent's first ALD diagnosis), and comparators had to be alive and without a diagnosis of ALD on that date. Comparators also had to be born in the same year and have the same sex as the ALD offspring to whom they were matched. Each comparator was selected at random (with replacement) from the general Danish population, meaning that a comparator could be selected for multiple offspring.

Follow-up

We followed offspring of patients with ALD and their matched comparators from the index date (date of parent's ALD diagnosis) until a diagnosis of ALD, death, emigration, or 31 December 2018, whichever occurred first. Offspring were, therefore, not necessarily followed from childhood but from the date of their confirmed exposure to their parent's ALD. Diagnoses of ALD were identified in the National Patient Registry, defined by an ICD-10 hospital discharge diagnosis code of K70.x, among which the codes K70.3 and K70.4 defined ALD cirrhosis. Offspring and comparators diagnosed with ALD were followed for all-cause mortality from the date of their ALD diagnosis until 31 December 2018.

Statistical analysis

We used landmark competing risk analysis to estimate the 10-year absolute and relative risk of ALD according to the current age of offspring and comparators [11]. This analysis used the cumulative

incidence function to compute the 10-year risk of ALD from age 25 years for offspring and comparators; then the same 10-year risk computations from age 26 years, 27 years, 28 years, and so on up to age 65 years, meaning that each offspring and comparator could contribute to multiple time windows. Death without ALD was considered a competing risk event. For example, offspring (and their matched comparators) were included in the analysis for age 25 years if their parent had been diagnosed with ALD before the offspring turned 25 years, and the offspring was still alive and without an ALD diagnosis at age 25 years. For the analysis of 10-year risk at age 25 years, follow-up began when the offspring turned 25 years and ended at age 35 years (censoring), at ALD diagnosis (outcome of interest), or at death (competing outcome), whichever came first.

The relative 10-year risk for offspring vs. comparators for the landmarks was computed at age 25 years, 26 years, etc., as the ratio of the absolute 10-year risks at that age between offspring and comparators. We used the pseudo-observation approach to compute the 95% confidence interval around the age-specific relative 10-year risks [12].

In subgroup analyses, we examined whether the absolute and relative 10-year risks at ages 45, 50, and 55 years varied according to the offspring's sex, the ALD parent's sex (mother/father/both parents had ALD) or the ALD parent's educational level. We did this by restricting the study population accordingly, and the absolute and relative 10-year risk estimates were computed as in the primary analysis of the total cohort.

To compare the survival after ALD diagnosis between those offspring and comparators who developed ALD, we plotted Kaplan-Meier survival curves adjusted for confounding using inverse probability of treatment weights [13]. We adjusted for age at the time of ALD diagnosis, sex, and calendar year of ALD diagnosis. We used Cox regression to estimate the mortality hazard ratio; this analysis adjusted for the same confounders by including them in the regression model.

Sensitivity analyses

Accurate estimates of absolute risk are important for decisions about screening for chronic liver disease and other interventions, so we undertook three sensitivity analyses. First, we wanted to address if ALD had been recorded as another chronic liver disease, so we widened the definition of ALD to encompass any chronic liver disease, following the definition in the Global Burden of Disease Project (ICD-10: B18, K70, K71.7, K73, K75.2, K75.4, K75.8, K75.9, K76, K77.8) [14].

Second, we addressed if ALD was recognized as an underlying or contributory cause of death in individuals not diagnosed during life. We used data from the Registry of Cause of Death to identify offspring and comparators who died from ALD without having been diagnosed with ALD during life and added those deaths to the ALD diagnoses made in life, with the date of ALD diagnosis being the date of death.

Third, we estimated the risk of ALD among the subset with an alcohol use disorder (AUD). In this analysis, we followed offspring of patients with ALD and their comparators from the first time they received a diagnosis of an alcohol-specific disorder other than ALD, as defined by Public Health England (ICD-10: F10.x, E24.4, E52.x, G31.2, G62.1, G72.1, I42.6, K29.2, K85.2, K86.0, O35.4, P04.3, Q86.0, R78.0, T51.0, T51.1, T51.9, Y15.x, Y90.x, Y91.x) [15]. We excluded offspring and comparators whose first such diagnosis was before the index date.

Data availability statement:

Electronic health records are, by definition, considered “sensitive” data in Denmark by the Data Protection Act and cannot be shared via public deposition because of information governance restrictions in place to protect patient confidentiality. Access to data is available only once approval has been obtained through the individual constituent entities controlling access to the data. The data can be requested via application to Statistics Denmark (www.dst.dk).

Results

We included 60,707 offspring of patients diagnosed with ALD from 1996 to 2018 in Denmark (Table 1). They had a median age of 31.8 years (IQR 23.4–39.4) when their parent was diagnosed with ALD, 8.4% were younger than 15 years and 51.4% were male. Most commonly, it was the father (65.9%) who was diagnosed with ALD, less commonly the mother (32.5%), and in 1.6% of offspring, both parents were diagnosed with ALD. There were 1,213,356 matched comparators (Table 1), and the number of unique individuals among the comparators was 1,012,887. Supplementary Figure S1 shows the number of offspring and comparators under follow-up according to current age.

ALD risk in offspring versus comparators

ALD was diagnosed in 385 of 60,707 offspring and 2,842 of 1,213,356 comparators during 0.7 and 14.0 million person-years of follow-up for an overall incidence rate ratio of 2.73 (95% CI 2.44–3.03) in offspring relative to comparators. For mortality, 1,405 offspring and 18,610 comparators died during the follow-up, yielding a mortality rate ratio of 1.52 (95% CI 1.44–1.60).

The absolute 10-year risk of ALD increased with age in both offspring and comparators, but it climbed faster and peaked at a younger age for the offspring. By age 50 years, the 10-year risk of ALD had reached 1.46% (95% CI 1.17–1.80), and it peaked at 1.66% (95% CI 1.16–2.30) for offspring aged 55 years (Figure 1, top). In other words, 1.66% of 55-year-old offspring were diagnosed with ALD between age 55 and 65 years. The corresponding 10-year risk for the comparators at age 55 years was 0.69% (95% CI 0.61–0.78), and their 10-year risk peaked at age 57 years at 0.81% (95% CI 0.68–0.97) (Figure 1, top).

The relative 10-year risk was around five at the younger ages and fell to around 1 (no increased risk) with increasing age (Figure 1, bottom). For example, at age 50 years, the relative 10-year risk was

2.41 (95% CI 1.92–3.02) and fell to 1.30 (95% CI 0.65–2.61) at age 60 years (Figure 1, bottom). Supplementary Figure S2 shows the absolute and relative 5-year risks of ALD: Patterns were the same as for 10-year risks, except that the absolute risks peaked at slightly older ages.

The subgroup analyses showed no difference in risk for male compared to female offspring, nor did the sex of the ALD parent influence the ALD risk in the offspring (Figure 2). If both parents had been diagnosed with ALD, the offspring's risk of ALD was noticeably higher at age 50 years. For age 45 and 55 years there was a similar pattern of higher risk in those with both parents diagnosed with ALD but estimates of relative risk were imprecise since there were few such offspring. For offspring aged 45 or 50 years, those whose ALD parent had attained only a primary level of education had a higher risk of ALD than those of an ALD parent with a secondary or higher level of education.

Survival after ALD diagnosis in offspring versus comparators

Offspring were younger at ALD diagnosis than comparators: Median age at ALD diagnosis was 47.4 years (IQR 42.3 – 52.0) in offspring and 48.9 years (IQR 44.0 – 53.8) in comparators, yet slightly more of them had developed cirrhosis (60.3 % vs. 58.7%). The survival probability after ALD diagnosis was similar in offspring versus comparators with an adjusted hazard ratio of 1.03 (95% CI 0.88–1.21) (Figure 3). Because the offspring were younger than comparators at ALD diagnosis, offspring died at a younger age: 45–49 years was the most frequent age at death in offspring compared with age 50–54 for the comparators (Figure 4). To put this differently, the median age at death was 49.6 years for offspring vs. 51.6 years for comparators.

Sensitivity analyses

When we expanded the definition of ALD to encompass chronic liver disease of any etiology, we identified 800 offspring and 9,657 comparators who developed chronic liver disease, and the incidence rate ratio was 1.66 (95% CI 1.55–1.79) vs. 2.73 in the primary analysis. The absolute 10-year risk for offspring aged 50 years rose from 1.46% in the primary analysis (ALD only) to 2.36% (95% CI 1.97–2.79) (any chronic liver disease). For comparators, the corresponding 10-year risk rose from 0.61% in the primary analysis to 1.34%, so the relative 10-year risk fell from 2.41 in the primary analysis to 1.76 (95% 1.47–2.10).

Adding ALD diagnoses recorded as cause of death and not during life had no notable effect on our findings. The number of ALD diagnoses among the offspring rose from 385 in the primary analysis to 426 (a 426/385 = 1.11-fold increase), but it rose by a similar amount among the comparators, from 2,842 to 3,129 (a 1.10-fold increase). The absolute 10-year risks rose by a similar amount in both groups, e.g., at age 55 it rose from 1.66% (95% CI 1.16–2.30) to 1.71% (95% CI 1.21–2.36) for the offspring and from 0.69% (95% CI 0.61–0.78) to 0.75% (95% CI 0.67–0.85) for the comparators. Thus, the relative 10-year risk changed only marginally, at age 55 from 2.40 (95% CI 1.66–3.46) to 2.27 (95% CI 1.59–3.24) (Supplementary Figure S3).

The risk of ALD was higher for offspring with AUD than for comparators with AUD (Supplemental Figure S4). We found that 3,152 offspring and 32,252 comparators were diagnosed with AUD during the follow-up. The proportion of men was 67.7% among offspring and 67.9% among comparators, and the median age (IQR) in the two groups was 36.9 years (27.0–44.9) and 37.6 years (26.3–45.8), respectively. The 1-year risks of ALD from diagnosis of AUD in the two groups were 1.6% (1.2–2.1) vs. 1.1% (1.0–1.2), the 5-year risks were 5.0% (4.2–5.9) vs. 3.3% (3.1–3.5), the 10-year risks were 7.6% (6.6–8.8) vs. 5.1% (4.9–5.4), and the 20-year risks were 12.6% (10.2–15.3) vs. 8.1% (7.5–8.8).

Discussion

This nationwide Danish study showed that offspring of patients with ALD had a nearly threefold increased risk of ALD. Their absolute risk of ALD was low, however, with the 10-year risk peaking at 1.66% at age 55 years with sharp declines before and after that age. Offspring were younger at the onset of ALD and had the same survival as other patients with ALD, so they died younger than other ALD patients.

We present the first study of the absolute and relative risk of ALD in offspring of patients with ALD. Our study has several strengths. It is nationwide, based on a large cohort of offspring of patients with ALD and follow-up is complete. Our study uses the general population as the comparator, thereby minimizing the risk of selection bias for comparators [16].

Our study has potential limitations, too. First, the parent-child link might be wrong. However, the misclassification of biological parent-child relations is only 1% and therefore negligible [5]. Nearly all children born after 1960 can be identified in the Danish Civil Registration System and although biological and adoptive relatives cannot be distinguished, only 1% of a Danish birth cohort is adopted [5].

Second, registered diagnoses of ALD may be wrong. However, the positive predictive value of the ALD diagnosis in the National Patient Registry has been high in validation studies, ranging from 71% to 91% when data from the registry was compared with medical chart review [17,18]. The comparable proportion with cirrhosis at ALD diagnosis for offspring and comparators indicates that our study was not affected by ascertainment bias: If offspring were more likely to be screened for ALD, we would expect a higher proportion of offspring to be diagnosed with non-cirrhotic ALD compared to comparators, and this was not the case. The comparable survival after ALD diagnosis

for offspring and comparators further indicates that the severity of ALD at diagnosis was similar for offspring and comparators.

Third, ALD might be misdiagnosed as another chronic liver disease, leading to underestimated risks of ALD. However, when we broadened the outcome definition of ALD to include any diagnosis code for chronic liver disease, the 10-year absolute risk for liver disease among 50-year-olds rose similarly for offspring and comparators: 0.90% and 0.73%, respectively. The similar, small increases in absolute risk for offspring and comparators with the broadened outcome definition indicate that misdiagnosis of ALD did not affect our findings. Also, the small increases in absolute risks observed reflect that alcohol contributes to about 60-70% of cirrhosis cases in Denmark, whereas other causes of chronic liver disease in Denmark include obesity/metabolic syndrome, chronic viral hepatitis, autoimmune hepatitis and rare causes such as hemochromatosis [17].

Fourth, ALD might not have been diagnosed at all, and we may underestimate the true risk of ALD. However, the combination of free access to healthcare in Denmark and the progressive natural history of ALD suggests that patients with ALD will eventually present to hospital if they continue their harmful alcohol consumption. We identified 11% more ALD diagnoses among the offspring when we added those that were only recorded as cause of death, but there were nearly as many extra diagnoses among the comparators (10%), and neither the absolute nor the relative risk of ALD changed materially (Supplemental Figure S3). Thus, failure to diagnose ALD in hospital did not affect our findings [19]. Finally, in the counterfactual scenario that the Danish population had been screened for ALD, more offspring (and comparators) would have been identified as having ALD. However, those additional diagnoses would represent cases of ALD that would never lead to a hospital diagnosis of ALD, and they are therefore less clinically relevant. We know from our previous work that the outcome we studied, a hospital diagnosis of ALD, is associated with a high risk for a liver-related death, and therefore it is relevant from a clinical perspective [20].

Other studies have examined the prognosis for offspring of patients with liver disease or AUD. First, our finding of a three-fold increased ALD risk in offspring is lower than the 12-fold increased risk of advanced fibrosis in first-degree relatives of patients with nonalcoholic fatty liver disease (NAFLD) cirrhosis in the study by Tamaki et al. [21]. This discrepancy in relative risk may be due to the definition of liver disease (liver fibrosis assessed with magnetic resonance elastography in the NAFLD study versus hospital diagnostic code for ALD in the present study). For example, offspring of ALD parents in our study would probably be even more likely than comparators to have ALD when assessed with elastography than when assessed as a hospital diagnosis because less than half of asymptomatic ALD detected by elastography may progress to symptomatic ALD [22]. Also, the selection of comparators was different between the studies (155 first-degree relatives of individuals without NAFLD versus a general population sample of more than 1 million in the present study). A recent registry-based study of liver-related outcomes in first-degree relatives of patients with biopsy-proven NAFLD found only a two-fold increased risk in the relatives [23]. However, the family occurrence of ALD and NAFLD may be different due to different genetic and environmental causes of these diseases.

Second, the nearly three-fold increased risk of ALD in offspring that we found is in line with the three-fold increased risk of alcohol-related disease and death in offspring of parents with AUD in a registry-based Danish study of AUD in 14,000 AUD offspring by Holst et al. [4]. The lack of association between the parent's sex and the offspring's ALD risk, and between the offspring's sex and ALD risk, is in line, too [4]. Our study extends Holst's study by estimations of the absolute risk and for the often-fatal outcome of ALD.

Several factors may cause the higher relative risk of ALD in offspring of individuals with ALD compared to comparators that we observed. The younger age at ALD diagnosis in offspring indicates that they began harmful alcohol consumption at a younger age than comparators did. They could

have easier access to alcohol and other addictive substances during adolescence, and early exposure to alcohol drinking is a significant risk factor for lifetime AUD development [24–26]. In addition, offspring of ALD patients could be more likely to experience stressful life events that increase the risk of AUD, such as parents' divorce, living in care homes, material deprivation, physical or sexual abuse, witnessing violence and, by our definition, parents' diagnosis of ALD and eventual physical and mental decline [25–28]. The higher risk of ALD in offspring of ALD parents of a primary compared to higher levels of education shows the importance of early-life socioeconomic circumstances for the risk of alcohol-related disease later in life [29]. The similar ALD risk in offspring and comparators after the age of 60 years (Figure 1, bottom) indicates that the prevalence of hazardous alcohol consumption is similar in offspring and comparators after 60 years. Heavy alcohol consumption is necessary for developing ALD, but genetic risk factors for ALD in the offspring may also contribute. For example, a recent study by Whitfield identified a genetic risk profile associated with a threefold higher relative risk of cirrhosis in individuals with a hazardous alcohol consumption [30]. The higher risk of ALD in offspring with both parents compared to one parent diagnosed with ALD (Figure 2) could be explained by higher environmental and genetic influences if two rather than one parent has ALD [31]. It is a limitation of our study that we were unable to investigate the relative importance of environmental and genetic factors. However, the prevalence of at-risk polymorphisms, primarily in the PNPLA3 gene, is likely the same in Denmark as in the rest of Europe [32], so there is no reason to consider Denmark anomalous and explain away our findings as due to genetic risk factors. We found that the risk of ALD was higher for offspring with an AUD diagnosis than for comparators with an AUD diagnosis (Supplemental Figure S4). This finding is consistent with a higher and/or more persistent alcohol consumption after AUD diagnosis among the offspring, but it is also consistent with a stronger genetic susceptibility to develop ALD among offspring of ALD parents. More importantly, the lack of information about the relative

importance of genes and environment should not stop anybody from preventing ALD; hazardous alcohol consumption is the main driver of ALD development.

Implications

We hope the results from this study can be used for clinical counseling. We can tell offspring of patients with ALD that their risk of developing ALD themselves is about three-fold increased, but—importantly—still small. Because the risk of ALD is small, we do not recommend that these offspring should be screened for liver fibrosis, but opportunistic screening may be considered, for example in offspring of two parents who have been diagnosed with ALD, and in offspring with AUD [33]. The younger age at ALD diagnosis in offspring, and their higher mortality irrespectively of ALD, indicates an earlier start of alcohol drinking, and therefore we suggest that offspring should be screened for AUD and referred to relevant treatment or social support. Offspring who develop ALD represent the loss of many life-years that, under different circumstances, might have been good.

Author contribution statement

PJ, GA and JW conceived the study idea. All authors contributed to design and methods. PJ conducted the analyses and GA wrote the first draft of the paper. All authors critically revised the manuscript.

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Table 1. Baseline characteristics of offspring of patients with alcohol-related liver disease in Denmark 1996 – 2018 and their matched comparators.

	Offspring	Comparators
Number	60,707	1,213,356
Sex, % men	51.4%	51.4%
Age at the time of parents' ALD diagnosis/matching		
Median (IQR)	31.8 (23.4–39.4)	31.8 (23.4–39.4)
< 15 years	5,087 (8.4%)	101,738 (8.4%)
15-24 years	12,694 (20.9%)	253,870 (20.9%)
25-34 years	19,161 (31.6%)	383,148 (31.6%)
35-44 years	17,225 (28.4%)	344,196 (28.4%)
45-54 years	5,938 (9.8%)	118,430 (9.8%)
55-64 years	596 (1.0%)	11,857 (1.0%)
≥ 65 years	6 (0.01%)	117 (0.01%)
Calendar year of birth		
Before 1960	3,755 (6.2%)	74,872 (6.2%)
1960-69	15,601 (25.7%)	311,633 (25.7%)
1970-79	19,225 (31.7%)	384,364 (31.7%)
1980-	22,126 (36.5%)	442,487 (36.5%)
Parent with ALD		
Father has ALD	40,020 (65.9%)	-
Mother has ALD	19,744 (32.5%)	-
Both parents have ALD	943 (1.6%)	-

ALD: Alcohol-related liver disease; IQR: Interquartile range

Figure 1. Absolute (top) and relative (bottom, with 95% confidence intervals) 10-year risks of alcohol-related liver disease (ALD) in offspring of patients with ALD and their matched comparators.

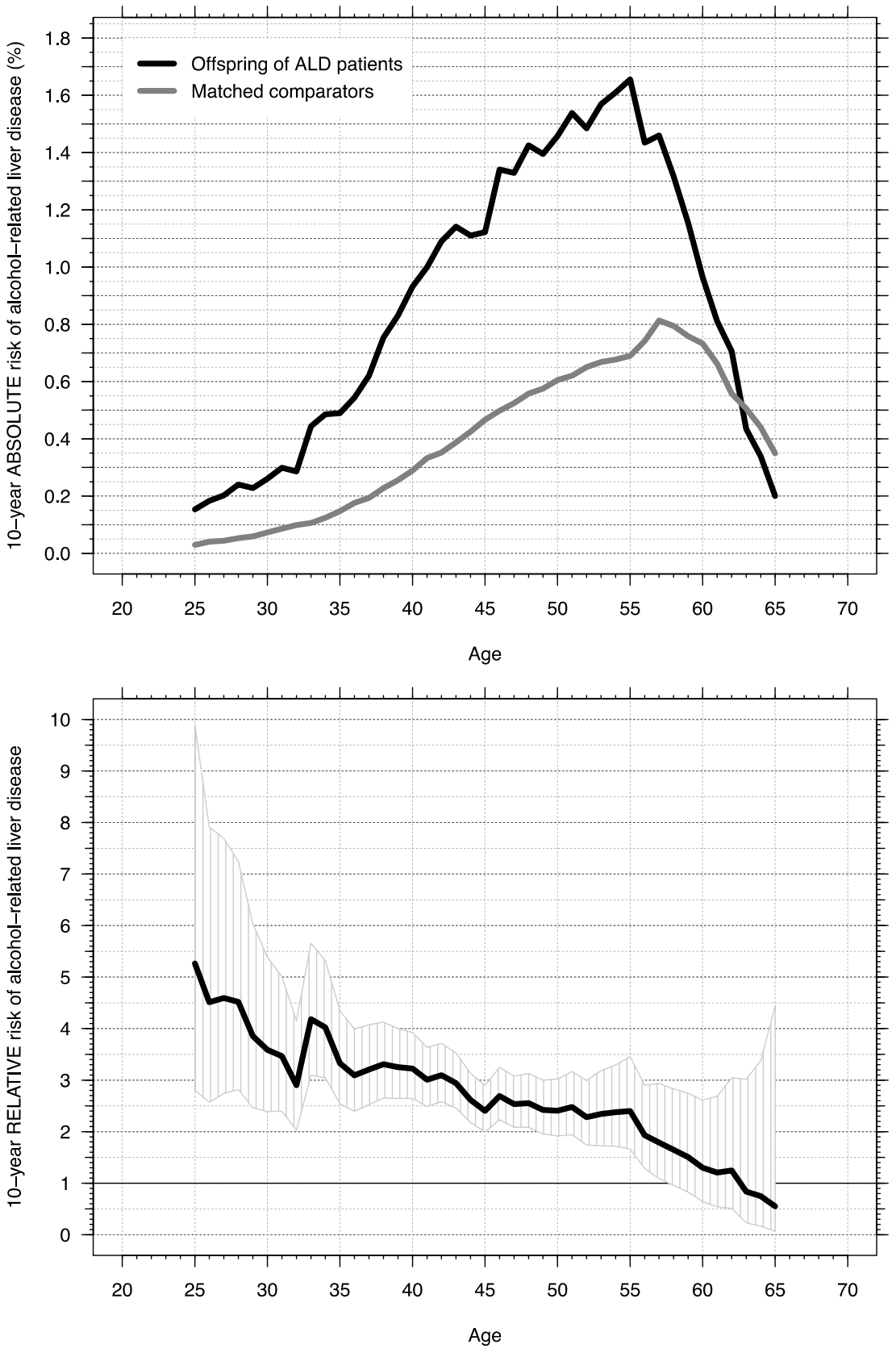


Figure 2. Absolute (right-hand column) and relative 10-year risks of ALD overall and within subgroups according to age of offspring of patients with ALD and their matched comparators, from ages 45 years, 50 years, and 55 years. The overall ("All") absolute and relative 10-year risks can also be seen in Figure 1.

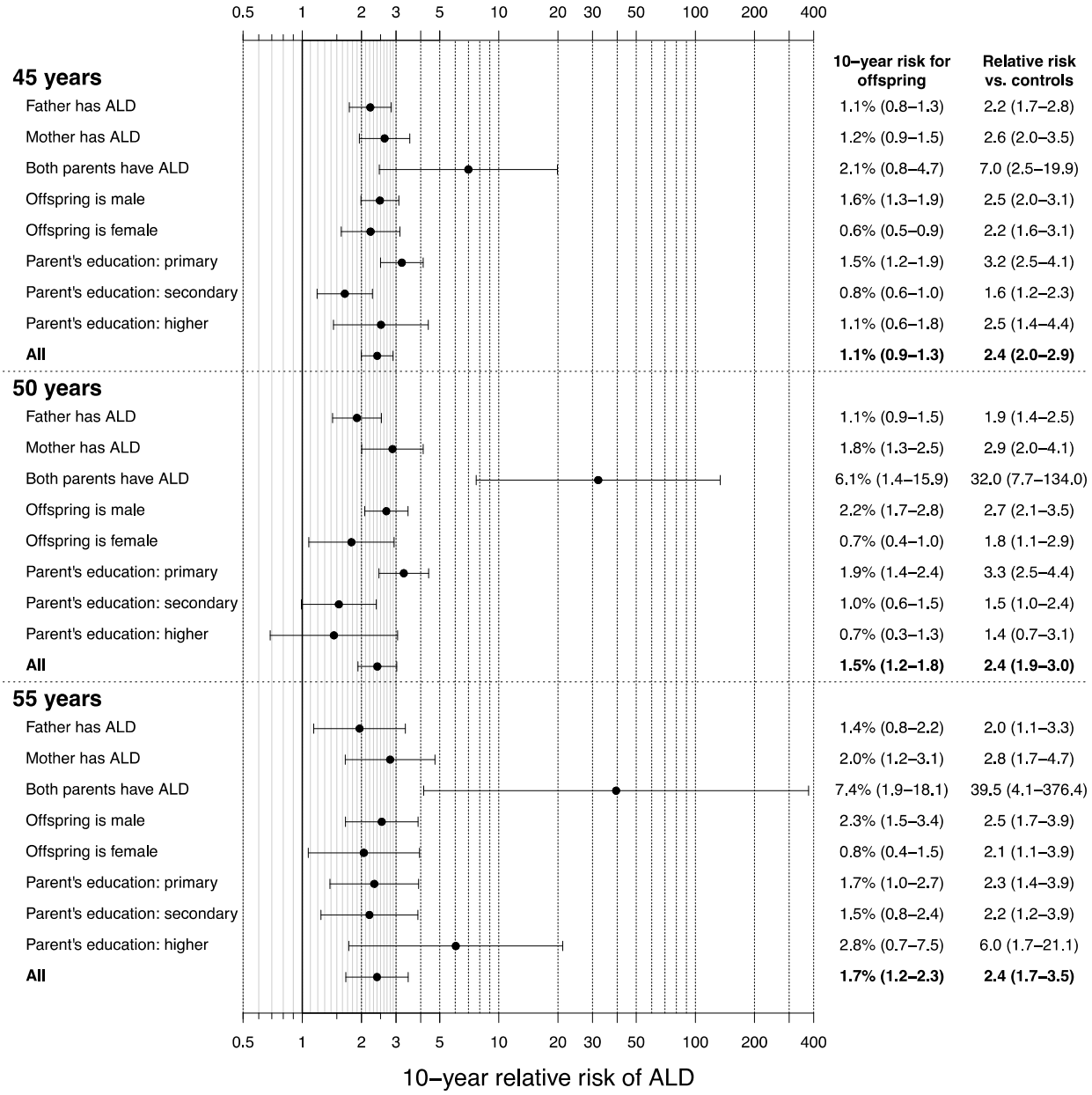


Figure 3. Survival probability from diagnosis of alcohol-related liver disease (ALD) in offspring of patients with ALD and their matched comparators, whose parents were not diagnosed with ALD. Survival probabilities are adjusted for confounding by sex, age, and calendar year.

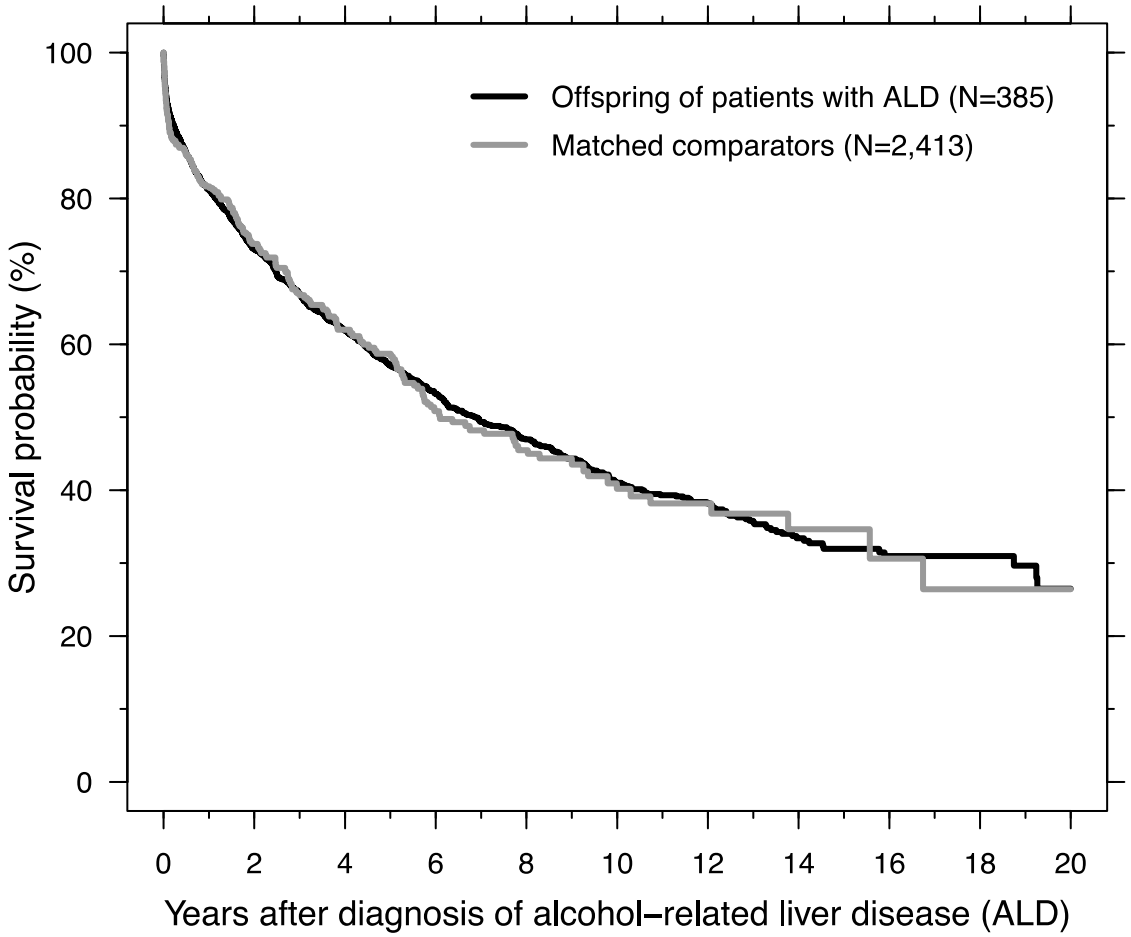
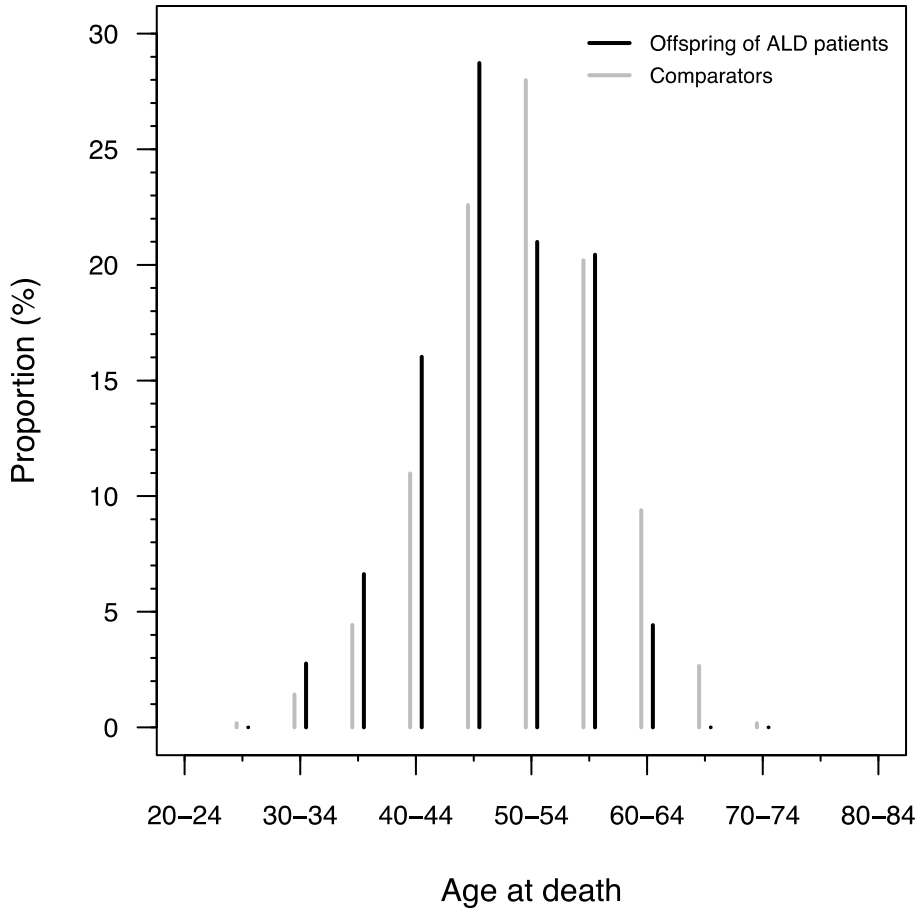


Figure 4. The distribution of ages at death after diagnosis of alcohol-related liver disease (ALD) in offspring of patients with ALD and their matched comparators, whose parents were not diagnosed with ALD.



Note: The figure shows that the offspring who develop ALD die at a younger age than the comparators who develop ALD.