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RESEARCH ARTICLE

Paternal Preconceptional Alcohol Use Disorder With the Offspring's Mortality Risk

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Introduction: Paternal preconceptional alcohol use may contribute to early pregnancy loss. However, the link between paternal preconceptional alcohol use disorder and long-term offspring's mortality risk remains unclear. This study examined the association of paternal preconceptional alcohol use disorder and recency of diagnosis with offspring's mortality and further stratified the mortality after the first year of birth by age.

Methods: This is a nationwide cohort study with 1,973,174 Danish births (1980–2012), with follow-up from birth until death; emigration; or December 31, 2016. Paternal conceptional alcohol use disorder was identified from Danish National Patient Register and Prescription Registry, categorizing recency of diagnosis into <1 year, 1 to <4 years, 4 to <8 years, and ≥8 years. Logistic regression estimated the ORs and 95% CIs for offspring mortality risk. All data were analyzed in 2023.

Results: Paternal preconceptional alcohol use disorder was associated with a 28% increased mortality after 1 year of birth (95% CI=1.09, 1.51), 23% increased infant mortality (95% CI=1.07, 1.42), and 23% increased odds of stillbirth (95% CI=1.06, 1.43). Paternal alcohol use disorder diagnosed <1 year before conception was associated with an 85%–111% increased risk of mortality in offspring aged 15–40 years. More recent alcohol use disorder diagnosis (i.e., 1 year before conception) had a higher risks of death from infectious and circulatory diseases in offsprings.

Conclusions: Offspring of fathers with alcohol use disorder before conception had higher mortality risk from birth to early adulthood, especially when alcohol use disorder diagnosis is close to conception. Current awareness regarding paternal preconceptional alcohol dependence use is insufficient. Promoting alcohol dependence avoidance, including educating men on the impact of alcohol on child health during prepregnancy examination, may help reduce or prevent long-term offspring mortality.

INTRODUCTION

Heavy alcohol consumption is linked to reduced male fertility,[1–3] probably owing to genetic and epigenetic sperm abnormalities,[3] decreased sperm count or quality,[1,4] and increased male fertility hormones levels.[4,5] These negative impacts are associated with difficulties in achieving a live birth.[4,6] Previous studies supported that men who consumed alcohol heavily during the week of conception increased the risk of early pregnancy loss and spontaneous abortion,[4,7,8] but few studies have examined the association of paternal preconceptional heavy alcohol use or

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alcohol use disorder (AUD) with subsequent offspring mortality risk. Offspring of fathers who consume alcohol once per week before conception had a 30% increased birth defects risk.[9] One study showed that paternal AUD diagnosed before birth had around 60% and double the risk of all-cause mortality and external causes of death in adolescence, respectively.[10] However, it remains uncertain whether paternal preconceptional AUD increases the long-term mortality risk in offspring. Furthermore, chronic and excessive alcohol consumption can cause liver damage and disrupt hormonal balance, affecting reproductive health and fertility. Recovery from these effects takes time.[2] Previous studies have primarily defined the paternal preconceptional period as <6 months before conception.[7,9] Filling this knowledge gap is important for preventing potential long-term health effects on offspring due to paternal alcohol dependence before conception.

This study addresses these important knowledge gaps using data from Denmark's population registers. The research question was how does paternal preconceptional AUD affect offspring mortality in the long-term? Because this study would like to cover a longer preconceptional period, it extended the preconception period to >8 years and also aimed to examine the long-term effects of paternal AUD. It further investigated the risk of infant mortality and stillbirth and stratified the mortality after the first year of birth by age.

METHODS

Study Population

This is a national, population-based cohort study of Danish national registries, comprising all births during 1980−2012 in Denmark who were followed until December 31, 2016 (registers description is in Appendix 1, available online).[11−15] The study was approved by the Danish Data Protection Agency (2013-41-2569). By law, no informed consent was needed for the analysis of anonymized register-based research in Denmark.

Measures

Paternal AUD was identified from the Danish National Patient Register and the Danish National Prescription Database.[14,15] Men diagnosed with alcoholic psychosis or alcoholism recorded in the patient register or those who redeemed alcoholism-related medication recorded in prescription database were classified as having AUD (Appendix Table 1, available online).[10] The recency of preconceptional AUD diagnosis was defined as the duration between the latest date of diagnosis and conception date and categorized into <1, 1 to <4, 4 to <8, ≥8 years (Appendix 2, available online).

This study obtained data on stillbirth from the Danish Medical Birth Register.[11] Records of death events were sourced from the Danish Register of Causes of Death.[12] Mortality outcomes were defined as follows: infant mortality (i.e., deaths within the first year of life), mortality after the first year of birth (i.e., excluding infant mortality), and all mortality throughout the follow-up period (i.e., all deaths). This study categorized the cause-specific infant mortality into 4 groups (Appendix Table 2, available online) and classified cause-specific overall mortality into 10 categories according to the European shortlist for Causes of Death (Appendix 2, available online, and Appendix Table 3, available online).[16]

Statistical Analysis

Logistic regression model with cluster-robust SEs estimation was used to account for multiple offspring per father and to examine the association of paternal preconceptional AUD and the recency of diagnosis with the risk of all mortality in the whole follow-up period, mortality after the first year of birth, infant mortality, and stillbirth using no paternal AUD as reference.[17] Furthermore, the association of paternal AUD and recency of diagnosis with mortality stratified by age group were examined (1 to <5, 5 to <15, 15 to <25, ≥25 years). Directed acyclic graph supplemented by literature was used to guide confounder selection (Appendix Figure 1, available online). Confounders controlled for included paternal age at birth (continuous), paternal educational attainment at birth (0−9, 10−14, ≥15 years), paternal annual income at birth (tertile of annual income in year of offspring's birth), born to an immigrant father (no, yes), calendar year of birth (5-year intervals in 1980−2009 and 2011−2012), and birth order (1, 2, ≥3) (Appendix 2, available online).

Several supplementary analyses were conducted. This study repeated the analysis on cause-specific infant and all mortality for the entire follow-up period. Cox proportional hazard model with a robust sandwich estimator was used to examine the risk of mortality outcomes in offspring and to test whether the results remained robust after considering the time from birth to death.[18] All offspring were followed from birth to date of death, emigration, or December 31, 2016 (or 1 year after birth for infant mortality analysis), whichever occurred first. Kaplan−Meier curve was performed to compare survival probability over time among different categories of AUD recency. The main analysis with a finer categorization of recency of diagnosis was also examined (i.e., <2, 2 to <4, 4 to <6, 6 to <8, >8 years). Other alcohol-attributed diseases were further included to identify fathers with preconceptional heavy alcohol use (Appendix Table 4, available online).[19] Furthermore, to account for the

common comorbidity of psychiatric disorders with AUD, the main analysis was restricted to offspring of fathers without other neuropsychiatric disorders (extracted from patient register) (Appendix Table 1, available online).[20,21] Simultaneously, subanalyses were conducted stratified by paternal liver diseases (extracted from patient register) (Appendix Table 1, available online), given the link between AUD, liver diseases, and impaired reproductive function.[22–25] In addition, stratified analysis by offspring's sex was conducted to examine the sex differences in the relation between paternal preconceptional AUD and mortality after first year of age and infant mortality. Because a U.S. study indicated no association between paternal alcohol consumption and spontaneous abortion after excluding maternal alcohol drinking,[26] stratified analysis by maternal AUD was conducted. Given the change in stillbirth definition in Denmark since April 2004 (from 28 to 22 completed weeks), stratified analyses based on the calendar year of April 2004 was conducted.[11] Finally, to address 10% missing data on SES and 10% for gestational age, multiple imputation procedure was performed by fully conditional specification method with an ordinal logistic regression model using paternal age at birth, calendar year of birth, birth order, paternal educational attainment and annual income at birth, stillbirth, infant mortality, and mortality as the predictors to generate 4 replications.

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and Stata 14 (Stata Corp, College Station, TX). All data were analyzed in 2023.

RESULTS

This study extracted 2,065,628 births during 1980–2012 from the Danish Medical Birth Register. A flow chart of the study population is given in Appendix Figure 2 (available online). Owing to the availability of the father's civil registration number (CPR) on stillbirth (i.e., available since 1991), this study restricted stillbirth analyses to liveborn after 1991. Among 1,378,349 eligible singleton births during 1991–2012, 5,081 (3.7 in 1,000 births) ended in stillbirth. Of 1,968,093 offspring born during 1980–2012, there were 8,522 (4.3 in 1,000 births) infant deaths, and 8,698 (4.4 in 1,000 births) deaths after the first year of birth. The corresponding rates were 5.5 in 1,000; 4.7 in 1,000; and 3.5 in 1,000 births in offspring with paternal preconceptional AUD, respectively. Overall mortality rates for offspring up to age 40 years (median=19.4 years [IQR=11.7–27.4]) were as follows: 65.4 in 100,000 person-years for AUD diagnosed <1year before conception; 63.9 in 100,000 person-years for 1 to <4 years; 45.6 in 100,000 person-years for 4 to <8 years, 43.7 in 100,000 person-years for ≥8 years; and 44.1 in 100,000 person-years for offspring without paternal preconceptional AUD. Offspring of fathers diagnosed with AUD tended to have lower paternal educational attainment and annual income and were born in later calendar years than offspring without paternal AUD (Table 1).

Table 1. Baseline Characteristics According to Offspring Exposure to Paternal Preconceptional AUD in Singleton Births

Baseline characteristics	No paternal AUD *n*=1,922,451 (%)	Paternal AUD *n*=50,723 (%)
Paternal age at child birth, mean+SD	32.0+5.8	32.2+6.4
Paternal educational attainment at birth		
Lower secondary or below	444,785 (23.9)	22,066 (44.7)
Upper secondary education	1,034,330 (55.5)	23,158 (46.9)
Tertiary education	383,474 (20.6)	4,113 (8.3)
Paternal annual income at birth[a]		
Lower-income class	591,017 (32.6)	24,526 (52.7)
Middle-income class	599,738 (33.1)	13,909 (29.9)
Upper-income class	622,237 (34.3)	8,112 (17.4)
Calendar year of birth		
1980–1985	307,154 (16.0)	2,074 (4.1)
1986–1990	282,226 (14.7)	3,371 (6.7)
1991–1995	323,068 (16.8)	4,644 (9.2)
1996–2000	313,127 (16.3)	8,845 (17.4)
2001–2005	293,025 (15.5)	11,563 (22.8)
2006–2010	293,025 (15.2)	14,328 (28.3)
2011–2012	106,046 (5.5)	5,898 (11.6)
Birth order		
1	854,112 (44.4)	22,865 (45.1)
2	716,581 (37.3)	17,131 (33.8)
≥3	351,758 (18.3)	10,727 (21.2)
Born to an immigrant father		
No	1,719,095 (89.4)	47,844 (94.3)
Yes	203,356 (10.6)	2,879 (5.7)

[a]Annual income was stratified by tertile distribution at the time of birth, that is, lower-income class (i.e., Tertile 1 of calendar year), middle-income class (i.e., Tertile 2 of calendar year), and upper-income class (i.e., Tertile 3 of calendar year).
AUD, alcohol use disorder.

Paternal AUD was also associated with a 28% (95% CI=1.09, 1.51) increased mortality risk after the first year of life (Figure 1). Paternal AUD diagnosed <1 year before conception was associated with 85%–111% increased risks of mortality at ages 15 to <40 years (Table 2). Kaplan–Meier survival curves also revealed that offspring of fathers diagnosed with AUD <1 year and 1 to <4 years before conception had significantly lower survival probabilities than offspring of fathers without AUD (Figure 2).

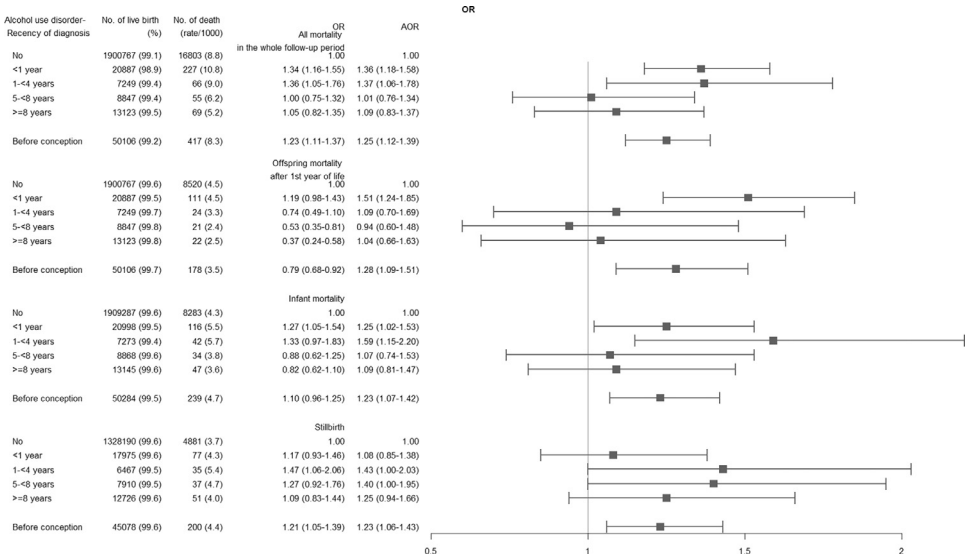

Figure 1. Abbreviate: OR=Odds ratio

Association of paternal preconceptional alcohol use disorders and recency of a diagnosis with the risk of stillbirth, infant mortality, mortality after 1 year of birth and all mortality in the whole follow-up period in offspring.

The cases of stillbirth have been removed before the calculation of after-birth mortality. The AOR models were adjusted for paternal age at birth, paternal educational attainment at birth, paternal annual income at birth, born to an immigrant father, calendar year of birth, and birth order.

Offspring of fathers diagnosed with AUD <1 year (OR=1.25, 95% CI=1.02, 1.53) and 1 to <4 years (OR=1.59, 95% CI=1.15, 2.20) before conception had higher risks of infant mortality than those without paternal AUD (Figure 1). Furthermore, paternal AUD was associated with increased stillbirth risk (OR=1.23, 95% CI=1.06, 1.43), compared with no paternal AUD. Paternal AUD diagnosed within 1 to <4 years and 4 to <8 years were associated with about 40% increased stillbirth risk. In contrast, paternal AUD diagnosed <1 year was not associated with stillbirth (Figure 1).

Regarding cause-specific mortality, paternal AUD was associated with an excess risk of offspring's infant death from the conditions originating in the perinatal period (OR=1.52, 95% CI=1.24, 1.86). Offspring of fathers diagnosed with AUD <1 year before conception had twofold risk of sudden infant death syndrome (SIDS) (description is presented in Appendix Table 2, available online) death (OR=2.44, 95% CI=1.71, 3.48) compared with unexposed offspring (Appendix Table 5, available online). Conversely, paternal AUD was negatively associated with infant death from congenital malformations (OR=0.63, 95% CI=0.45, 0.89). Paternal AUD was associated with a 72% increased risk of offspring's death from unnatural death, including transport accidents, other external causes of accidental injury, and intentional self-harm (detailed description is presented in Appendix Table 3, available online) (95% CI=1.36, 2.16). Paternal AUD diagnosed <1 year before conception was associated with twofold risk of death from infectious diseases and circulatory diseases (Appendix Table 6, available online).

Other supplementary analysis yielded similar findings to those of the main analyses (Appendix Tables 7–11, available online). This study observed a higher stillbirth risk when both of the parents were diagnosed with AUD than for offspring of fathers with AUD only (Appendix Table 12, available online). Male offspring tended to have a higher risk of infant mortality than female offspring, whereas female offspring had a higher risk of mortality after the first year of birth than male offspring (Appendix Table 13, available online). Stratifying the analysis by the calendar year of April 2004, stillbirth risk among offspring of fathers diagnosed with AUD <1 year before conception was 1.33 (95% CI=1.01, 1.76) before April 2004 and 0.69 (95% CI=0.42, 1.11) after April 2004 (Appendix Table 14, available online). Compared with offspring without paternal AUD, the association between paternal AUD diagnosed >8 years before conception and stillbirth was stronger among offspring of fathers with liver diseases (OR=2.15, 95% CI=1.17, 3.95) than those of fathers without liver diseases (OR=1.11, 95% CI=0.80, 1.54) (interaction p-value=0.06) (Appendix Table 15, available online).

DISCUSSION

This study found that paternal preconceptional AUD was associated with an increased mortality risk from birth to early adulthood. Paternal AUD diagnosed <1

Table 2. Association of Paternal Preconceptional Alcohol Use Disorders With the Mortality Risk Stratified by Age

Paternal alcohol use disorders	Live birth (%)[a]	Overall deaths (rate/1,000)[a]	Crude OR (95% CI)	Adjusted OR (95% CI)[2]
1 to <5 years				
No	1,907,243 (99.9)	2,044 (1.1)	1.00	1.00
Diagnosed before conception	50,225 (99.9)	59 (1.2)	1.10 (0.85, 1.42)	1.19 (0.90, 1.58)
Recency of diagnosis				
<1 year	20,967 (99.9)	31 (1.5)	1.38 (0.97, 1.97)	1.26 (0.85, 1.86)
1 to <4 years	7,268 (99.9)	5 (0.7)	0.64 (0.27, 1.54)	0.81 (0.34, 1.94)
4 to <8 years	8,858 (99.9)	10 (1.1)	1.05 (0.57, 1.96)	1.14 (0.57, 2.28)
≥8 years	13,132 (99.9)	13 (1.0)	0.92 (0.54, 1.59)	1.35 (0.76, 2.39)
5 to <15 years				
No	1,905,497 (99.9)	1,747 (0.9)	1.00	1.00
Diagnosed before conception	50,192 (99.9)	33 (0.7)	0.72 (0.51, 1.01)	1.11 (0.78, 1.57)
Recency of diagnosis				
<1 year	20,950 (99.9)	17 (0.8)	0.89 (0.55, 1.43)	1.12 (0.69, 1.81)
1 to <4 years	7,261 (99.9)	7 (1.0)	1.05 (0.50, 2.21)	1.64 (0.78, 3.45)
4 to <8 years	NA	NA	0.62 (0.26, 1.48)	1.06 (0.44, 2.54)
≥8 years	NA	NA	**0.33 (0.12, 0.89)**	0.73 (0.27, 1.95)
15 to <25 years				
No	1,902,294 (99.8)	3,202 (1.7)	1.00	1.00
Diagnosed before conception	50,129 (99.9)	63 (1.3)	**0.75 (0.58, 0.96)**	**1.43 (1.10, 1.88)**
Recency of diagnosis				
<1 year	20,905 (99.8)	45 (2.1)	1.28 (0.95, 1.72)	**1.85 (1.35, 2.53)**
1 to <4 years	7,252 (99.9)	9 (1.2)	0.74 (0.38, 1.42)	1.12 (0.50, 2.49)
4 to <8 years	NA	NA	**0.27 (0.10, 0.72)**	0.65 (0.24, 1.74)
≥8 years	NA	NA	**0.23 (0.09, 0.54)**	0.97 (0.40, 2.33)
≥25 years				
No	1,900,767 (99.9)	1,527 (0.8)	**1.00**	**1.00**
Diagnosed before conception	50,106 (100.0)	23 (0.5)	**0.57 (0.38, 0.86)**	**1.60 (1.04, 2.47)**
Recency of diagnosis				
<1 year	20,887 (99.9)	18 (0.9)	1.07 (0.67, 1.71)	**2.11 (1.30, 3.42)**
1 to <4 years	NA	NA	0.52 (0.17, 1.60)	0.83 (0.21, 3.34)
4 to <8 years	NA	NA	0.28 (0.07, 1.13)	1.01 (0.25, 4.04)
≥8 years	NA	NA	NA	NA

Note: The cases of stillbirth have been removed before the calculation of after-birth mortality outcomes.
Note: boldfaced refers to p-value<0.05
[a]According to the Statistics Denmark policy, the cases <5 cannot be reported.
[b]The models were adjusted for paternal age at birth, paternal educational attainment at birth, paternal annual income at birth, born to an immigrant father, calendar year of birth, and birth order.
NA, not available.

year before conception was associated with an 85%−111% increased mortality risk in offspring aged 15 to <40 years. The increased infant mortality risk was primarily from conditions originating in the perinatal period and from SIDS, whereas the increased risk of all mortality was mainly from unnatural death such as transport accidents, other external causes of accidental injury, and intentional self-harm. Offspring of fathers diagnosed with AUD <1 year before conception also had a higher risk of death from infectious and circulatory diseases. The association of paternal AUD diagnosed ≥8 years before conception with stillbirth was evident only among offspring with paternal liver diseases.

In this study, paternal preconceptional AUD was associated with a 25% and 28% increased odds of all mortality and mortality after the first year of life, respectively. Offspring of fathers with AUD diagnosed <1 year before conception had a higher risk of death from circulatory diseases. Previous studies suggested that paternal alcohol intake may influence fetal and postnatal organ development[27] and that seminal fluid from father can impact the offspring's glucose tolerance and blood pressure in adulthood.[28] Recent studies have shown that paternal alcohol consumption before conception increased the risk of congenital heart defects in offspring by approximately 44%−48%.[29,30] One putative mechanism is that paternal alcohol exposure may influence

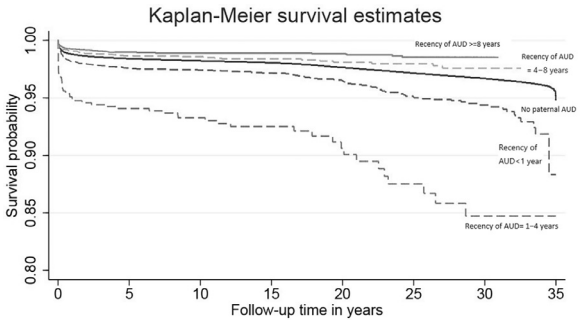

Figure 2. Survival probability among offspring unexposed to paternal preconceptional AUD versus exposed to recency of a paternal preconceptional AUD.

The adjusted survival probability was averaged across the distribution of the covariates, for paternal age at birth, paternal educational attainment at birth, paternal annual income at birth, born to an immigrant father, calendar year of birth, and birth order.

AUD, alcohol use disorder.

epigenetic processes, impacting gene expression and altering histone modifications related to heart development.[29,30]

In this study, paternal AUD diagnosed <1 year before conception was associated with an increased risk of death from infectious diseases. A recent Swedish study reported a 66% higher risk of death from infectious diseases in the offspring of fathers with alcohol and drug dependence use.[31] In mice models, paternal preconceptional alcohol exposure was found to disrupt nerve growth factor,[32] and nerve growth factor plays a relevant role in the immune response.[33] Taken together, paternal AUD impacts the innate and the acquired immune system, thereby increasing the risk of death from infectious disease.

Consistent with previous study, paternal AUD increased the risk of death from unnatural causes in offspring.[10] Two Swedish cohort studies found that paternal preconceptional AUD increased death from external causes, with high excess risks of death from drug-related causes, accident, and suicide.[10,34] Another recent study found that paternal alcohol consumption was associated with an increased risk of offspring's later suicide and violent death, but these effects disappeared after adjusting for their offspring's risky use of alcohol or other lifestyle risk factors, for example, smoking and low emotional control.[35] The association of paternal preconceptional AUD with death from unnatural causes may be mediated by factors related to the children's risky behaviors.

Furthermore, in this study, paternal preconceptional AUD was associated with an increased risk of infant death from the condition originating in the perinatal period. Paternal preconceptional and chronic alcohol exposure was associated with an increased risk of intrauterine fetal growth restriction and loss of placental efficiency.[36,37] An in vivo study showed that paternal preconceptional alcohol intake affects offspring fetal−placental growth.[36] Chronic alcohol exposure may affect sperm histone post-translational modifications and may lead to long-lasting alterations in the developmental programs regulating placental function.[38] Seminal plasma composition can also influence the maternal uterine environment, by altering blastocyst development and placental size and affecting embryonic development in mice.[28] These factors collectively contribute to offspring fetal−placental growth and may lead to the infant death from the condition originating in the perinatal period.

Intriguingly, paternal AUD was negatively associated with the risk of infant mortality from congenital malformations. In an vivo study, paternal preconceptional alcohol exposures were associated with exencephaly in fetuses,[39] which could be detected in the first-trimester scan. A human study also supported that worse semen quality, for example, low semen concentration, sperm count, and motility, increased the risk of congenital birth defects.[40] Some parents may undergo induced abortion after the early detection of malformation after the prenatal test.

Offspring of fathers diagnosed with AUD 1 to <4 years before conception had an increase in stillbirth risk by 40%, whereas no such increased risk was observed for paternal AUD diagnosed <1 year before conception. Chronic alcohol consumption by men could negatively impact sperm quality and function, contributing to alcohol-induced oxidative damage and epigenetic changes in sperm DNA.[2,39] Despite the possibility of functional recovery, the process takes time and depends on the organ's degree of injury.[41] Poor sperm quality has been linked to spontaneous abortions in partners.[9,42−44] Improved imaging technology in the last 2 decades has enhanced early malformation detection,[45] leading some parents to opt for induced abortion after screening.[45] Taken together, offspring whose fathers are diagnosed with AUD <1 year before conception may exhibit birth defects earlier than stillbirth or may undergo induced abortion. Therefore, the offspring who remained in this study might be relatively healthier and exhibit longer survival times. This potential selection bias due to the depletion of susceptible may have biased the estimate toward the null.

Interestingly, in this study, the association of paternal AUD diagnosed ≥8 years before conception with stillbirth only appeared among offspring with paternal liver diseases, whereas offspring of fathers diagnosed with both AUD and liver diseases had a higher risk of infant mortality than those of fathers without liver diseases.

Excessive alcohol use has been associated with liver damage,[2,46] which may influence reproductive function and fertility.[22] Prior studies supported that men with liver diseases often exhibit lower semen volume and serum testosterone and an increase in abnormal sperm morphology.[47,48] In animal study, rats with liver fibrosis demonstrated severe reproductive dysfunction, and the restoration of liver fibrosis did not coincide with the recovery of the reproductive system.[49] Collectively, offspring of fathers diagnosed with AUD diagnosed ≥8 years before conception may be linked to liver damage, thereby increasing stillbirth risk.

Limitations

This nationwide population-based cohort study examined the paternal preconceptional AUD and the recency of diagnosis with stillbirth and early-life mortality. With a large sample size and long follow-up, it enabled detailed analysis of time-specific records of exposure, cause-specific mortality, and mortality risk across age groups. Using Danish Registries to retrieve prospective data from almost all Danish residents with nearly complete follow-up minimized recall bias. However, several limitations should be noted. First, this study was limited by a lack of data on the exact amount of alcohol consumed, and thus this study cannot examine the dose−response relationship of paternal preconceptional alcohol intake with the risk of stillbirth and mortality in the offspring. The recency diagnosis date before conception could not confirm whether fathers had ceased alcohol use in more recent years before conception. However, this recency was used to assess whether the earlier exposure, that is, preconceptional AUD 4−8 years, was associated with a similar risk to the exposure in the recent years. Duration and severity of AUD were also unknown, limiting their impact assessment. Second, misclassification bias of both AUD and the recency of diagnosis may occur. Some cases of the paternal AUD might not have been identified or misdiagnosed, and the medication data were only available from 1995 onward. However, this misclassification might have biased the risk estimates toward null. Third, fetal alcohol spectrum disorders were not included in the analysis. Offspring exposed to alcohol during fetal life may have an increased risk of developing fetal alcohol spectrum disorders, which might be associated with stillbirth and infant mortality risk,[50] potentially influencing the results. Fourth, robust error technique was used to address intramatched group dependence from the same father, but residual confounding factors, for example, uncontrolled genetics and lifestyle characteristics, may still be present. Fifth, despite the large sample size, the number of events for cause-specific mortality is relatively small, and the results may be due to chance. Similarly, the study's lack of statistical power to analyze outcomes in finer recency of diagnosis categories is a limitation. Sixth, lack information on the alcohol-related lifestyle, for example, paternal use of tobacco and substance, which may lie in the pathway between paternal AUD and offspring's stillbirth and mortality, also limited the study. Seventh, >33% of stillborn offspring had missing information on their sex. Consequently, this study was unable to conduct a stratified analysis on the association between paternal AUD and stillbirth risk. Finally, about 10% of the SES and gestational age data are missing in the complete case analysis. Nevertheless, multiple imputation techniques were used to input the missing data, and the results remained consistent with those of the completed cases analysis.

CONCLUSIONS

The findings of this study suggest that paternal preconceptional AUD was associated with a 25% increased risk of offspring's stillbirth and subsequent long-term mortality throughout the early decades of life. Offspring of fathers with AUD have higher risks of infant mortality, particularly from perinatal conditions and SIDS, as well as increased all-cause mortality from unnatural causes. Paternal AUD diagnosed <1 year before conception was associated with an increased risk of death from infectious and circulatory diseases. The global emphasis on raising awareness of alcohol dependence among men who are trying to conceive is insufficient, so promotion of reduced alcohol dependence among men of childbearing age should be encouraged to reduce the risk of offspring's stillbirth and mortality. There needs to be a strengthening of targeted public health campaigns and educational initiatives to specifically address men, emphasizing the implications of alcohol dependence on the health of their future children during premarital or prepregnancy physical examination. This study also underscores the significance of specialized care and monitoring for offspring born to fathers with AUD or alcohol-related diseases before conception.

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SUPPLEMENTAL MATERIAL

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