Alcohol Use Disorders

- in relation to Alcohol Consumption, Psychiatric Co-morbidity, and Suicide

PhD thesis by

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THIS THESIS IS BASED ON FOUR PUBLICATIONS:

Paper I

Flensborg-Madsen T, Knop J, Mortensen EL, Becker U, Grønbæk M:
Amount of alcohol consumption and risk of developing alcoholism in men and women. *Alcohol and Alcoholism* 2007; 42(5):442-447.

Paper II

Flensborg-Madsen T, Knop J, Mortensen EL, Becker U, Makhija N, Sher L, Grønbæk M:
Beverage preference and risk of alcohol use disorders – a Danish prospective cohort study. *Journal of Studies on Alcohol and* Drugs 2008; 69(3):371-7.

Paper III

Flensborg-Madsen T, Mortensen EL , Knop J, , Becker U, Sher L, Grønbæk M:
Co-morbidity and temporal ordering of alcohol use disorders and other psychiatric disorders. Results from a Danish longitudinal study. [*Comprehensive Psychiatry: In press*]

Paper IV

Flensborg-Madsen T, Knop J, Mortensen EL, Becker U, Sher L, Grønbæk M:
Alcohol use disorders increase the risk of completed suicide - irrespective of other psychiatric disorders. A longitudinal cohort study. *Psychiatry Research* 2009; 167:123-130.

PREFACE

This PhD thesis is submitted in fulfilment of the requirements for the PhD degree at the Faculty of Health Sciences, University of Copenhagen, Denmark. The work was carried out at the H:S Institute of Preventive Medicine from 2006 to 2007, at Columbia University in 2007, and at the National Institute of Public Health from 2008 to 2009. The project was supported by grants from the Lundbeck Foundation and from the Danish Medical Research Council.

I wish to express my sincere thanks to my supervisors Morten Grønbæk, Joachim Knop, and Erik Lykke Mortensen for being an invaluable team of supervisors. Especially I owe thanks to Joachim for initiating the PhD-project, for selecting me to carry it out, and for his always optimistic and everlasting confidence in me. I owe my thanks to Morten for his inspiration to investigate new aspects of alcohol research, for sharing his scientific insight with me, and for providing me with an excellent environment for doing this project. And I owe thanks to Erik for his engagement and his presence and for always being ready with constructive criticism. Although Ulrik Becker is not an official supervisor on this project, he has certainly acted as such, providing me with valuable insights and raising important questions.

During my stay at Columbia University I worked at Department of Psychiatry where I would like to sincerely thank Leo Sher for giving me the opportunity to work with him and do both epidemiological and clinical research. This was a very memorable stay and it lead to the publication of several papers in this PhD thesis. Without funding, the stay at Columbia University would not have been possible wherefore I would like to thank: Augustinus Fonden, Knud Højgaards Fond, Oticon Fonden, Fonden til Lægevidenskabens Fremme, Christian og Otillia Brorsons Rejselegat for yngre videnskabsmænd- og kvinder, and the Faculty of Health Sciences at the University of Copenhagen for their financial support that made it possible.

I would like to thank Joav Merrick for being both my mentor and my good friend during my time as a PhD-student and most likely for many years ahead. It was because of his encouragement that I got the chance to go to Columbia University.

I thank the steering committee and the staff of the Copenhagen City heart Study for letting me use the data and thanks go to every person who participated in the Copenhagen City Heart Study and thereby made this thesis possible.

Thanks go to all my colleagues and friends at the National Institute of Public Health for contributing to an inspiring and stimulating workplace. Working here I was always among good friends who made every day enjoyable and exciting. Finally, a special thanks to Thomas, Julie, Emilie, and Rasmus for making it all worthwhile.

Trine Flensborg-Madsen, December 2008

1. INTRODUCTION

Alcohol use disorders (AUD) are recognised and classified as mental disorders, with AUD often defined as consisting of the two following conditions: Harmful use of alcohol and alcohol dependence[1]. *Harmful use* may not necessarily be a result of daily consumption of alcohol but could also be due to binge drinking that could result in road traffic accidents, domestic violence, perpetuation of poverty etc. (1). The World Health Organization (WHO) describes it as "A pattern of alcohol use that is causing damage to health, and the damage may be physical (e.g. liver damage) or mental (e.g. episodes of depression)" (2). Harmful use is frequently associated with adverse social consequences of various kinds and it is often criticized by others (3). *Alcohol dependence* is described by the WHO International Classification of Diseases 10 (ICD-10) as "a cluster of physiological, behavioural and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviours that once had greater value" (3). Thus, the central feature of alcohol dependence is the overpowering desire to consume alcohol. AUD has in research been classified in several other ways using Diagnostic and Statistical Manual of Mental Disorders (DSM) (4) and has been defined using AUD-scales such as MAST (5), CAGE (6), and AUDIT (7). However, in the present thesis the meaning of the concept is considered a composition of harmful use and alcohol dependence.

AUD is among the most prevalent psychiatric disorders in the general population (8;9), and in many countries it is a major medical and social problem that goes largely untreated (10). In addition, individuals with AUD often have co-morbid psychiatric disorders, contributing to the increased risk of both morbidity and mortality (11-18). It has been estimated that 585.000 Danes have a harmful alcohol intake and that 140.000 can be classified as alcohol dependent (19), and in a study of Danish general practitioners it was found that 3.9% of contacts were due to patients with a large alcohol intake (20). A WHO study of 14 countries found that 5% of all patients consulting health case services in primary health care were having alcohol dependence (21), and WHO estimated that worldwide, there are an estimated 70 million people who have AUD - 78% of whom remain untreated (22). Based on register data from secondary health care, a prevalence of AUD of 7.6% was found in the Copenhagen City Heart Study (CCHS), which is the study used in the present thesis.

This thesis will focus on the association between alcohol intake and AUD (**Papers I and II**), the association between alcohol intake and psychiatric disorders, the psychiatric co-morbidity of AUD (**Paper III**), and the association between AUD and suicide (**Paper IV**). It is structured as follows: First, a background section on AUD and the aims of each of the sub-studies are presented, followed by a brief summary of the methods and results. Thereafter, a discussion of the results and of potential biases is presented; and finally the main conclusions are summarized alongside a short discussion of the perspectives. Efforts have been made only to summarize what is already mentioned in the four papers, and consequently reference is made to the papers in the appendix for more detailed information.

[1] The term alcoholism is at times used as a synonym for AUD; however, in the present thesis it is strived only to use the term AUD since alcoholism can be interpreted as stigmatizing.

2. BACKGROUND OF ALCOHOL USE DISORDERS

To briefly make clear the overall background of AUD, this section includes short descriptions of biological, hereditary, and environmental factors that constitute the complex dynamics of AUD.

2.1. Biology of alcohol intake

Alcohol is absorbed from the stomach and duodenum and is distributed within the body's water compartment. Two enzymes are of major importance for the metabolization of alcohol. Alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde, which is converted to acetate by the enzyme aldehyde dehydrogenase (ALDH).

$$\text{Alcohol} \xrightarrow{\text{ADH}} \text{Acetaldehyde} \xrightarrow{\text{ALDH}} \text{Acetate} + H_2O$$

Increased concentrations of acetaldehyde, which might be caused by an inhibition of ALDH, can result in unpleasant acetaldehyde symptoms, which can vary from facial flushing, sweating, and mild headache to severe cardiovascular collapse, arrhythmias, unconsciousness and convulsions. ALDH is one of the most studied biochemical components in the research of AUD and variation in ALDH has been shown to predict AUD (23). Disulfiram (Antabuse), a pharmacological treatment of AUD, is an effective inhibitor of ALDH and, thus, creates an aversion to alcohol by accumulation of the toxic substance acetaldehyde.

Studies have highlighted a range of genes with impact on diverse brain systems with potential relevance for the vulnerability to AUD (24;25). Intake of alcohol stimulates the opiod system in releasing endorphins, which activate the dopaminergic reward system (26); especially the binding of opiates to the μ-opioid receptors results in heightened dopamine levels (27;28). And individual differences in the sensitivity of the opiod system have been suggested as a reason for differences in risk of AUD (29). Dopamine plays an important role in the rewarding effects of alcohol, since consumption of alcohol activates dopamine neurons that lead to a release of neurotransmitters in the limbic system and, thus, a positive reinforcement and reward (30). Whereas dopamine mainly acts as a modulator in the reward system, two other neurotransmitters, GABA and glutamate (NMDA), are responsible for the sedative effects of alcohol, and can create adaptive changes that involve hyper-excitability with symptoms such as arousal, anxiety, and sleeplessness when alcohol is rapidly withdrawn (31). Numerous other physiological systems have been found to be important for the vulnerability to AUD. The fact that specific genes play a part in this vulnerability has been proven in epidemiological studies with the use of twin and adoption studies.

2.2. Heritability of alcohol use disorders

Family, twin, and adoption studies have demonstrated that genetic factors play an important role in the development of AUD. First, children of parents with AUD have been found to be three to five times more likely to develop AUD than the biological children of non-AUD parents (32). Second, seven out of eight major twin studies of AUD in men have found a significantly greater concordance in monozygotic twins compared to dizygotic

twins (33), and twin studies of AUD in women also found this concordance (34). Third, adopted children of biological parents with AUD have been found to have the same four-fold enhanced risk for AUD as does children raised by their biological parents with AUD (35). Generally, the proportion of risk of AUD explained by genes is estimated to be between 40 and 60% (36;37). Despite strong evidence that genetic effects do contribute to the development of AUD, multiple factors complicate the identification of specific genes involved in the predisposition. Many genes are thought to contribute to AUD susceptibility, such as for example *ADH1B* and *ADH1C* genotypes (38), and various genes are likely to contribute to AUD in different individuals. Although it is possible that a small number of genes might directly influence the development of AUD, it is more likely that the relevant genes influence a range of genetically influenced intermediate characteristics, endophenotypes, that subsequently affect the risk of heavy drinking and thereby AUD (36;39). Each of these endophenotypes is likely to reflect multiple genes and to interact with both genetic and environmental factors. A range of endophenotypes has been described as potential contributors towards the development of AUD. Individual characteristics such as devotion and conservatism (40), have been shown to be inversely associated with AUD while factors such as social anxiety disorder (41), sensation seeking behaviour (42;43), seasonal affective disorder (44), the personality trait of novelty seeking (45), and low sense of coherence (46) are positively related to AUD. It is, however, difficult to separate results on personality traits and AUD due to the fact that AUD can cause personality change (47).

2.3. Environmental factors and alcohol use disorders

Genetic epidemiological studies have indicated that a large part of the liability to prematurely alcohol drinking and intoxication in adolescents is environmental (48;49). Using data from a twin study it was shown that the magnitude of genetic influences on adolescent alcohol use varied up to five-fold in different environments, suggesting that some environments may intensify the manifestation of genetic predispositions (50). It has been suggested that prenatal alcohol exposure may operate to increase risk of excessive alcohol use in two ways (51): Through antisocial outcomes related to fetal alcohol syndrome (52) and through pharmacological vulnerability due to prenatal alcohol exposure (53). Especially animal studies have suggested that fetal exposure to alcohol may lead to the development of specific drug sensitivities (53-55). Parenting practices (56) and peer influences (57) have been shown to be important factors in early life. Later in life, factors such as low education and low social status have been associated with AUD in several studies (58-61). Among women, poor social support was found to be associated with a greater likelihood of alcohol dependence and abuse (62). And neighbourhood drug availability and norms were associated with alcohol dependence in an American study (63). Sociodemographic factors have proven to modify alcohol misuse in several studies of groups of individuals from different ethnic groups (64;65).

The exploration of AUD is, as illustrated in the above sections, an area of great complexity which involves both genetic and environmental factors. In this thesis, five specific areas of interest were chosen that were within reach of the available epidemiological data. Hence, aspects of both determinants, co-morbidity and outcomes of AUD were investigated; the background and aims of each being described below.

3. BACKGROUND AND AIMS OF THE SPECIFIC SUB-STUDIES

3.1. Alcohol consumption and risk of alcohol use disorders

In many respects, alcohol can be considered the causal agent in developing AUD because it must be present for AUD to occur. Several studies have found associations between heavy drinking patterns and increased risk of alcohol-related consequences such as drunk driving, injuries, job problems, and crime (66-70). However, although exposure to alcohol is a necessary component in the causal network leading to AUD, the empirical relationship between amount and frequency of consumption and AUD is not known. The Danish National Board of Health's sensible drinking limits are 14 and 21 drinks per week for women and men, respectively. These limits are based on thorough reviews of studies related to the health effects of alcohol. For public health purposes, the association between weekly intakes of alcohol and the later risk of AUD would thus be an important contribution to the scientific basis of creating guidelines on sensible drinking limits.

In Paper I, the aim was to investigate the associations between amount and frequency of alcohol intake and the risk of AUD.

3.2. Beverage preference and risk of alcohol use disorders

Several studies have suggested that different types of alcoholic beverages have different health-related outcomes, such as subjective health, risk of stroke, hip fracture, lung cancer, prostate cancer, gastric cancer, alcohol-induced cirrhosis, dementia, and mortality.(71-83). According to alcohol-related outcomes it has been found that moderate wine drinkers appear to be at lower risk of becoming heavy and excessive drinkers compared to moderate beer drinkers (84). Moreover, the exclusive beer and spirits drinkers and drinkers of all three beverages were found to be more likely than the other drinker types to consume five or more drinks on a single occasion and to engage in delinquent behaviour (85). In addition, studies have found associations between beer-drinking and unsafe behaviours such as driving while intoxicated (68;86;87). Finally, certain lifestyle and personality factors such as: social, intellectual, and personal functioning (88), diet (89), education (90), and quality of life (83), have been shown to be associated with beverage preference. Therefore it is plausible that preferred type of alcoholic beverage is associated with the later risk of AUD. This has, however, not yet been investigated.

In Paper II, the aim was to analyze whether preferred type of alcoholic beverage is associated with the later risk of developing AUD.

3.3. Alcohol consumption and risk of psychiatric disorders

Denmark and several other countries have sensible drinking limits of 14 drinks and 21 drinks per week for women and men respectively. These limits are primarily set up based on the risk of alcohol-related physical diseases and mortality. But whereas 14 and 21 drinks per week is a large amount of alcohol in relation to the physical influences of alcohol on the body – results concerning the relationship between amount of alcohol and the risk of psychiatric disorders are diverse (91-99).

The aim of this sub-study (under preparation for publication) was to investigate the association between amount of alcohol intake and the risk of mood disorders, psychotic disorders, anxiety disorders, personality disorders, drug abuse and psychiatric disorders in general.

3.4. Co-morbidity of alcohol use disorders and other psychiatric disorders

A high prevalence of co-morbid psychiatric disorders in individuals with AUD has been verified in a number of epidemiological studies (8-10;100-103), and it has also been found that AUD is more prevalent among people with psychiatric disorders than in the general population (104-107). The co-occurrence of AUD and other psychiatric disorders may reflect 3 different scenarios: (1) AUD contributes to the development of the disorder, (2) the disorder contributes to the development of AUD, and (3) the development of both AUD and the disorder reflects common etiologic factors. For most psychiatric disorders, all three scenarios are likely. It is however, for public health purposes, important to investigate both the sizes of this co-morbidity in addition to the temporal ordering of the disorders, since individuals with co-morbid AUD often have a poorer treatment response and a worse course of illness over time (104;108-111). Due to these clinical consequences, research that aim to improve the understanding of the patterns of co-morbidity are clearly essential to help guide treatment as well as prevention and intervention. However, studies aiming to investigate both co-morbidity and temporal ordering of AUD and other psychiatric disorders are lacking.

In Paper III, the aim was to investigate psychiatric co-morbidity and temporal ordering of AUD, focusing on: Mood disorders, psychotic disorders, anxiety disorders, personality disorders, drug abuse, in addition to psychiatric disorders in general.

3.5. Alcohol use disorders and suicide

Suicide is an enormous public health problem around the world. In 1998 suicide was estimated to represent 1.8% of the total burden of disease (112) and in 2001 the WHO reported that self-inflicted injuries including suicide accounted for more than 800,000 deaths world-wide per year (113). Knowledge of the epidemiology of suicide is a necessary prerequisite for developing prevention programs. And evidence of an association between alcohol use and suicidal behaviour has been reported in numerous studies (114-117). However, since data on risk factors of completed suicide are rarely available, most studies have focused on suicidal ideation or attempted suicide. Suicide is often considered to be a consequence of a psychiatric disorder (114;115), and research has demonstrated a series of psychiatric disorders to be risk factors for suicidal behaviour (114;118-121). Furthermore, studies have shown (including paper III) that co-morbid psychiatric disorders are frequent in patients with AUD. In terms of prevention it would thus be valuable to know the size of increased risk of suicide among individuals with AUD and to know whether other psychiatric disorders are necessary factors for this increased risk.

In Paper IV, the aim was to assess the association between AUD and completed suicide and to assess the role of other psychiatric disorders in this association.

4. METHODS

4.1. Source of data: The Copenhagen City Heart Study

The study aims were conducted using the Copenhagen City Heart Study (CCHS). CCHS is an ongoing series of studies conducted in the Danish population and initiated in 1976, when a random sample of men and women above 20 years of age and living in the Copenhagen area was invited to participate. The sample was randomly drawn from the Central Population Register, by use of the unique personal identification number, and invited by letter to answer self-administered questionnaires in the years 1976-78. The number of participants was 14,223, with a response rate of 74 %. This examination was followed by three more examinations in the years 1981-83 (CCHS-II) (number of participants 12,698; response rate 70%), 1991-94 (CCHS III) (number of participants 10,135; response rate 61%) and 2001-03 (CCHS-IV) (number of participants 6,238, response rate 50%). The last examination, CCHS-IV, was not used in this thesis as the follow-up time of the registers ended in 2002. All follow-ups were supplemented with younger participants in order to keep the population large and representative. Detailed descriptions of the study have been published elsewhere (122-124).

4.2. Assessment of alcohol exposure

Information on amount, frequency, and type of alcohol intake was obtained from CCHS-I-III where participants were asked in multiple-choice format to describe their alcohol habits. In CCHS-I, however, the weekly alcohol intake had to be calculated: As in CCHS-II and III, participants in CCHS-I were asked whether they "hardly ever/never", "monthly", "weekly", or "daily" drank alcohol, but only if this intake was daily, was the average daily intake recorded. Thus, an absolute amount of consumed alcohol was obtainable only for persons stating a daily alcohol intake. Therefore the weekly intake in CCHS-I was calculated by means of a series of regression models estimated from CCHS-II. These were previously constructed by Becker et al. (125) and include the explanatory variables age, sex, alcohol intake patterns and weekly alcohol intake. In all three waves, the average weekly intake of beer, wine and spirits was summed to the total alcohol intake (with one bottle of beer being approximately equivalent to the alcohol contents of one glass of wine or one glass of spirits – assuming each drink contains 12 g of alcohol).

The advantage of obtaining data on alcohol intake prospectively in several waves is that data on alcohol intake can be updated so that each person is characterized anew in each of the following examinations; this was done in Paper II.

4.3. Assessment of exposure and endpoints by linkage to national registers

All persons invited to CHHS I-III were followed by linkage with Danish registries using the unique personal identification number. The *Danish Hospital Discharge Register* (126) contains information on all admissions to Danish hospitals since 1976; the *Danish Psychiatric Central Register* (127) contains records of all individuals who have been admitted to a psychiatric hospital in Denmark since 1969; the *WINALCO-database* (128) contains records of all individuals treated for alcohol problems in the Alcohol Unit, Hvidovre Hospital – an outpatient clinic for alcoholics covering the greater Copenhagen

and Frederiksberg municipalities since 1954; and the *Danish Causes of Death Register* (129) contains information on causes of death of all Danish residents who died in Denmark since 1943. Diagnoses in the registers are classified according to the World Health Organization's International Classification of Diseases (ICD) using the eighth revision until 1994, and the tenth revision from 1994 and onwards.

Endpoints in the present thesis were, depending on the aim, either: AUD, suicide, or psychiatric disorders (divided into the groups: Mood disorders, psychotic disorders, anxiety disorders, personality disorders, and drug abuse). The diagnosis of AUD was defined by registration in the WINALCO-database or by having an alcohol-related diagnosis in either the Danish Hospital Discharge Register or the Danish Psychiatric Central Register. In Paper I, the following alcohol-related diagnoses were used: The categories of *alcohol psychoses* (291) and *alcoholism* (303) in the ICD-8 system and the category of *Mental and behavioural disorders due to use of alcohol* (F10) (except from acute intoxication) in the ICD-10 system. In Papers II to IV, only the subcategories *alcoholism* (303) in the ICD-8 system and *harmful use* (F10.1) and *dependence syndrome* (F10.2) in the ICD-10 system were used to describe alcohol use disorders. Table 1 gives an overview of the number of individuals registered with AUD (as defined in Papers II-IV) in each register and of the overlap of registrations within the three registers.

Table 1. Number of individuals with AUD in each register and percentage of AUD registrations captured in the other registers.

	WINALCO - Database	Danish Psychiatric Central Register	Danish Hospital Discharge Register
WINALCO-Database (%)	**685**	139 (14.8)	111 (10.8)
Danish Psychiatric Central Register (%)	139 (20.3)	**941**	228 (22.3)
Danish Hospital Discharge Register (%)	111 (16.2)	228 (24.2)	**1024**

Suicide was defined using the Danish Causes of Death Register as: "Suicide and self-inflicted injury" (ICD-8: E950-959) or "Intentional self-harm" (ICD-10: X60-84). And psychiatric disorders were defined as registration in either the Danish Hospital Discharge Register or the Danish Psychiatric Register with the following diagnostic categories being used:

- AUD	**Paper I:**	ICD-8 (291, 303), ICD-10 (F10 minus "Acute intoxication")
	Papers II-IV:	ICD-8 (303), ICD-10 (F10.1, F10.2)
- **Mood disorders**:		ICD-8 (296, 300.4, 298.0), ICD-10 (F30-34, 38, 39)
- **Psychotic disorders**:		ICD-8 (295, 297, 298.1-9, 299), ICD-10 (F20-29)
- **Anxiety disorders**:		ICD-8 (300.0, 300.2, 300.3), ICD-10 (F40-43)
- **Personality disorders**:		ICD-8 (301), ICD-10 (F60)
- **Drug abuse**:		ICD-8 (304), ICD-10 (F11-19 – for only harmful use and dependence)
- **Any psychiatric disorder other than AUD**:		ICD-8 (28, 30, 31), ICD-10 (F1, F2, F3, F4, F5, F6, F7, F8, F9), minus AUD diagnoses.

4.4. Statistical analysis

The main analyses used to estimate the associations between exposures and outcomes were Cox proportional hazard regression (130). By including age as the time variable the estimates were adjusted for confounding by age. Subjects were followed from their date of entry, when they answered their first questionnaire between 1976-93, to the date of the first registration of the outcome, death, disappearance, emigration, or until the end of follow-up (January 2002) – whichever occurred first. The assumption of proportional hazards was tested for the main exposures by adding a time-dependent covariate (log t) to the regression model and testing the significance of this interaction with significance defined as $p<0.05$. No violations were detected. All analyses were performed using SAS software package SAS 9.1.

In contrast to time-fixed covariates, the main exposures and possible confounding factors taken from CCHS were time-dependent variables as they were measured repeatedly over time in 1976-78, 1981-83, and 1991-1993, with the number of observations and the time between the observations varying between subjects. As the value of those are likely to change over time, updated measures of exposures and confounders were used from Paper II and onwards. In these analyses we prospectively assessed the risk of outcome in between examination increments based on determinations of covariates derived from the preceding questionnaire. Technically, this means that each person was treated as several observations, where persons were characterized anew in each of the following examinations, and information on all observation intervals was pooled as if the information recorded at each interval were a new observation. In case of missing data the last observation was carried forward.

For further information on the statistical methods used, please refer to the Papers I-IV.

4.5. Ethics

The Danish ethics committee for the City of Copenhagen and Frederiksberg approved CCHS (#01-144/01), and all participants gave written informed consent. Data from registers was available through the Danish unique personal identification numbers that were anonymized so that no individuals could be identified. According to Danish law, retrospective register studies do not require approval by the Committee on Scientific Ethics.

5. RESULTS

5.1. Amount and frequency of alcohol consumption and risk of alcohol use disorders (Paper I)

Among the 14,223 respondents from the baseline of the Copenhagen City Heart Study (CCHS-I), 879 persons (6.22%) were registered with AUD. For women, the risk of AUD increased dose-dependently with increased weekly alcohol intake. Compared to women whose alcohol intake were less than 1 drink per week, the adjusted hazard ratio (HR) for women drinking 1-7 drinks per week was 1.83 (95% confidence interval (CI): 1.16,2.88), and the adjusted HR for women drinking 8-14 drinks per week was 3.11 (95% CI: 1.88-5.12) (Figure 1). For men, the risk of AUD was not significantly increased for weekly intakes under 21 drinks compared to men whose alcohol intake was less than 1 drink per week. Only for intakes of more than 21 drinks per week the risk was significantly increased (Figure 2).

Figure 1. Hazard ratios (HRs) of AUD for women according to amount of weekly alcohol intake. Hazard ratios were adjusted for confounders that were significant in the model: smoking.

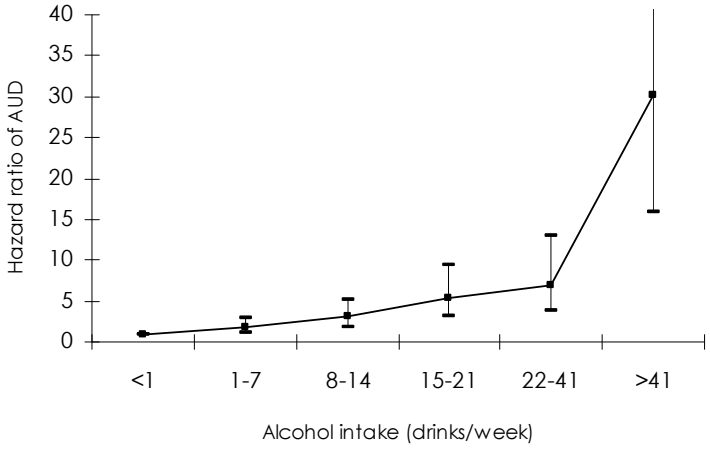
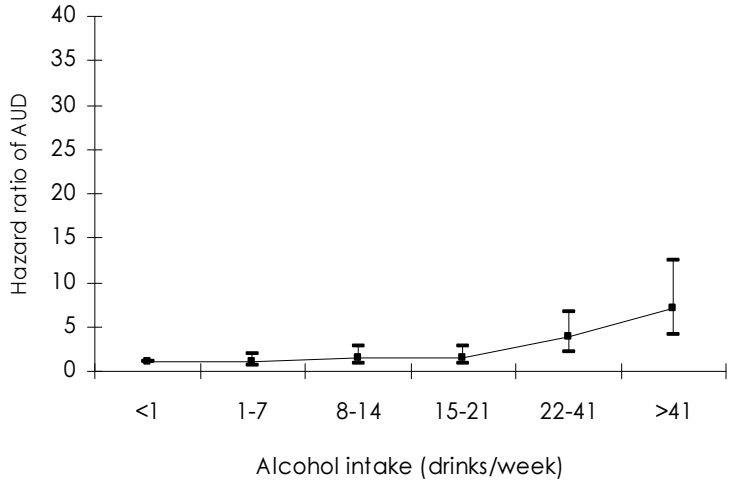


Figure 2. Hazard ratios (HRs) of AUD for men according to amount of weekly alcohol intake. Hazard ratios were adjusted for confounders that were significant in the model: smoking, exercise, and marital status).



The frequency of alcohol intake was positively associated with AUD for both men and women in analyses that did not adjust for weekly alcohol intake. Using never-drinkers as the reference group, women significantly increased their risk of AUD by drinking monthly (HR=1.69, 95% CI: 1.04-2.76), while men increased their risk of AUD by drinking daily (HR=3.42, 95% CI: 2.03-5.77) (Figure 3 and 4).

Figure 3. Hazard ratios (HRs) of AUD for women according to frequency of alcohol intake. Hazard ratios were adjusted for confounders that were significant in the model: smoking.

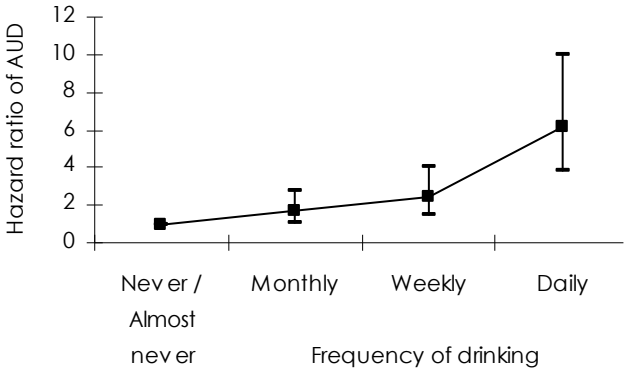
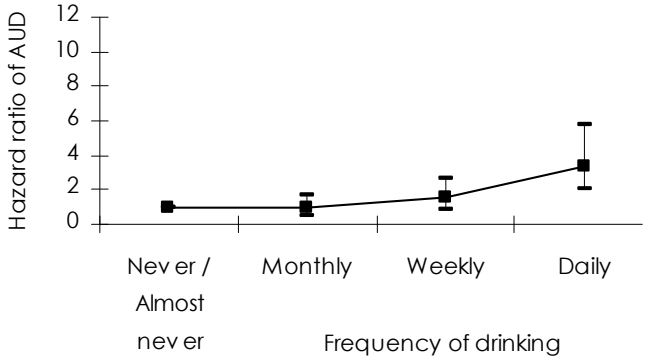


Figure 4. Hazard ratios (HRs) of AUD for men according to amount of weekly alcohol intake. Hazard ratios were adjusted for confounders that were significant in the model: smoking, exercise, and marital status).

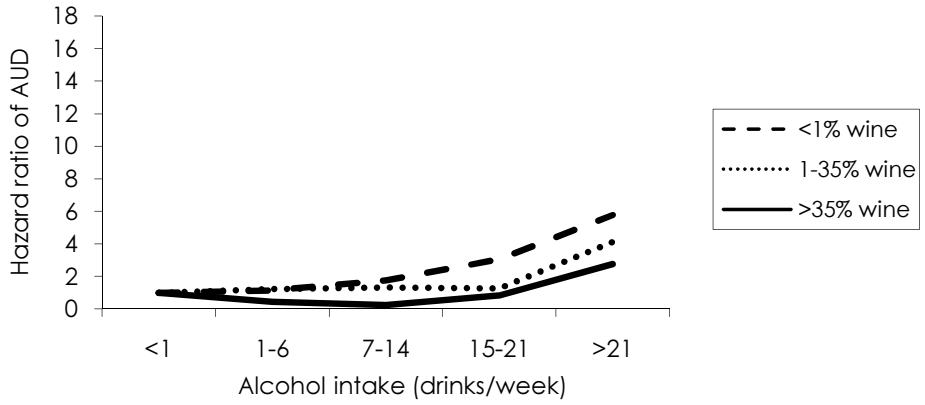


5.2. Beverage preference and risk of alcohol use disorders (Paper II)

Of the 18,146 individuals completing at least one of the three questionnaires in CCHS-I-III, 1,200 (6.6%) were registered with AUD. For both genders, subjects who did not include wine in their alcohol intake had an increased risk of developing AUD compared to subjects that did include wine (Figure 5 and 6). Consumption of more than 35% beer increased the risk of AUD in women for all classifications of weekly alcohol intake compared to drinking <1% beer and 1-35% beer. The percentage of beer intake did not influence the risk of AUD for men. And the percentage of spirits was not associated with AUD for either women or men.

Figure 5. Hazard ratios (HRs) of AUD for women according to percentage of wine in total alcohol intake and according to total alcohol intake. Hazard ratios are set to 1.0 among non-drinkers and are adjusted for smoking, cohabiting status, income, and education.

Figure 6. Hazard ratios (HRs) of AUD for men according to percentage of wine in total alcohol intake and according to total alcohol intake. Hazard ratios are set to 1.0 among non-drinkers and are adjusted for smoking, cohabiting status, income, and education.



5.3. Amount of alcohol consumption and risk of psychiatric disorders

Among the 18,146 individuals completing at least one of the three questionnaires in CCHS-I-III, 965 (5.3%) individuals were registered with mood disorders, 382 (2.11%) with psychotic disorders, 333 (1.84%) with anxiety disorders, 602 (3,32%) with personality disorders, 295 (1.63%) with drug abuse, and 2092 (11.53%) were registered with some kind of psychiatric disorder other than AUD. While, in Paper I, the risk of AUD increased dose-dependently with increased weekly alcohol intake, the risk of psychiatric disorders was not as directly associated to alcohol intake. For women, the overall pattern shows that large amounts of alcohol increases the risk of psychiatric disorders, mainly anxiety disorders and psychiatric disorders in general (Figure 7). For men there seems to be a protective effect of drinking some alcohol every week, and this is the case for all psychiatric disorders (Figure 8).

Figure 5. Hazard ratios (HRs) of different psychiatric disorders for women according to amount of weekly alcohol intake. Hazard ratios were adjusted for smoking, co-habitation status, education, and income.

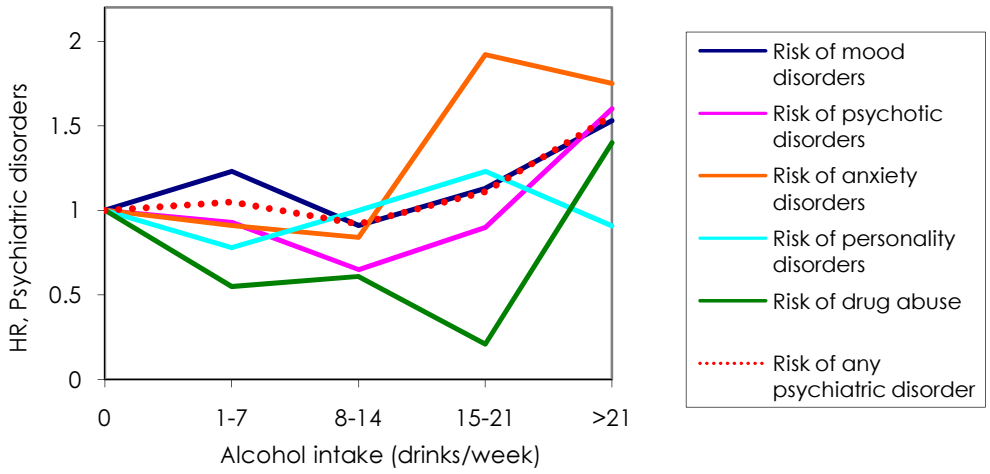
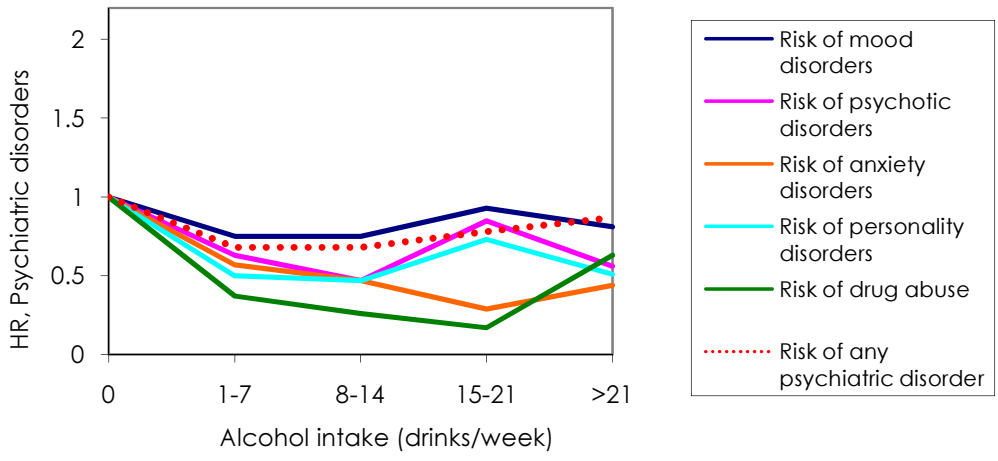


Figure 6. Hazard ratios (HRs) of different psychiatric disorders for men according to amount of weekly alcohol intake. Hazard ratios were adjusted for smoking, co-habitation status, education, and income.



Dividing the weekly alcohol intake into intakes *below* of *above* the Danish sensible drinking limits of 14 and 21 drinks per week respectively for men and women showed that for women, intakes above the recommendation increased the risk of especially anxiety disorders and psychiatric disorders in general (Table 2).

For men, there was no increased risk of any psychiatric disorder with intakes above the sensible drinking limits. Conversely, although the estimates are not significant, there seems to be a pattern of a protective effect of drinking above the recommendations (Table 3).

Table 2. Hazard ratios (95% Confidence Interval) of psychiatric disorders for women according to drinking above the recommended alcohol intake per week. Hazard ratios were adjusted for smoking, co-habitation status, education, and income.

Number of drinks per week	Risk of mood disorders	Risk of psychotic disorders	Risk of anxiety disorders	Risk of personality disorders	Risk of drug abuse	Risk of any psychiatric disorder (other than AUD)
0-14	1	1	1	1	1	1
> 14	1.18 (0.83-1.68)	1.30 (0.72-2.32)	2.00 (1.31-3.04)	1.22 (0.73-2.04)	1.02 (0.43-2.38)	1.27 (0.98-1.66)

Table 3. Hazard ratios (95% Confidence Interval) of psychiatric disorders for men according to drinking above the recommended alcohol intake per week. Hazard ratios were adjusted for smoking, co-habitation status, education, and income.

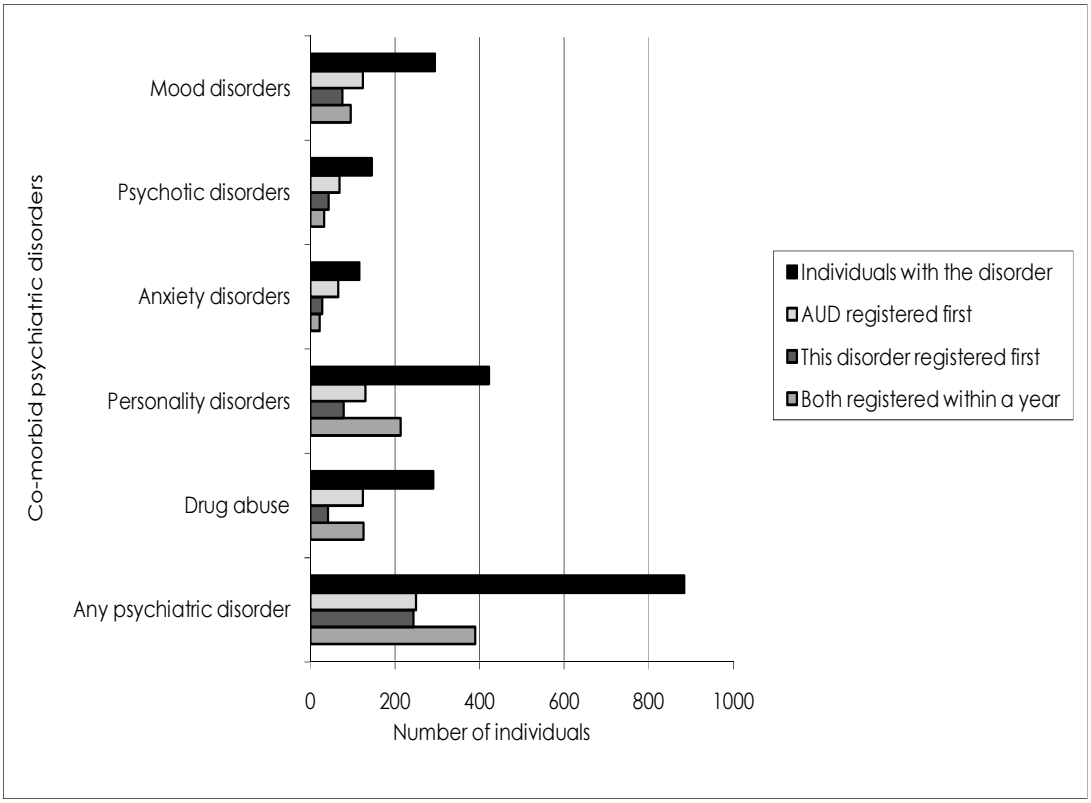
Number of drinks per week	Risk of mood disorders	Risk of psychotic disorders	Risk of anxiety disorders	Risk of personality disorders	Risk of drug abuse	Risk of any psychiatric disorder (other than AUD)
0- 21	1	1	1	1	1	1
> 21	0.98 (0.68-1.41)	0.79 (0.45-1.40)	0.79 (0.42-1.50)	0.84 (0.48-1.47)	1.56 (0.90-2.69)	1.16 (0.91-1.47)

The results from this sub-study in addition to the results from Paper I shows that alcohol is not a common risk factor of both AUD and other psychiatric disorders. This led to the objective of the next paper, Paper III, in which the focus was to investigate the co-morbidity of AUD and other psychiatric disorders.

5.4. Co-morbidity and temporal ordering of alcohol use disorders and other psychiatric disorders (Paper III)

Among the 1,200 individuals in CCHS-I-III registered at least once with AUD, 50.3% had a lifetime co-morbid psychiatric disorder. The sizes of this co-morbidity are shown in Figure 9. First-time AUD registration was most likely to precede first-time registration of mood disorders, psychotic disorders, anxiety disorders, personality disorders, and drug abuse in individuals with co-morbid psychiatric disorders to AUD (Table 6). When analyzing the risks over time in Cox proportional hazard regression analyses, it was found that the risk of developing one of the psychiatric disorders in individuals already registered with AUD was greater than the risk of developing AUD in individuals who were already registered with another psychiatric disorder – especially among individuals with anxiety disorders, personality disorders, and drug abuse.

Figure 9. Characteristics of the 1756 individuals with AUD.



5.5. Alcohol use disorders and suicide – the influence of psychiatric disorders (Paper IV)

Of the 23,189 individuals invited to CCHS-I-III, 209 (0.90%) committed suicide, while 1756 (7.6%) were registered with AUD. Individuals registered with AUD were at an increased risk of committing suicide compared to individuals never registered with AUD (crude HR 7.98, 95% CI: 5.27-12.07). All five groups of psychiatric disorders were significant confounders in the association between AUD and suicide and altered the hazard ratio when included in the analysis. Adjusting for all psychiatric disorders at the same time reduced the risk of completed suicide among individuals with AUD to 3.23 (CI: 1.96-5.33) (Table 4).

Table 4. Hazard ratios (95% Confidence Interval) of completed suicide according to AUD. Reference group consists of individuals never registered with AUD.

Adjusted for:	**Hazard ratio**
Unadjusted	7.98 (5.27-12.07)
Sex	7.36 (4.82-11.23)
Lifestyle covariates*	5.91 (3.76-9.27)
Psychotic disorders	6.88 (4.48-10.55)
Anxiety disorders	7.17 (4.69-10.97)
Mood disorders	4.72 (2.99-7.44)
Personality disorders	4.54 (2.73-7.55)
Drug abuse	5.95 (3.71-9.56)
All five disorders**	3.44 (2.10-5.64)
Other psychiatric disorders†	6.02 (3.80-9.56)
All psychiatric disorders††	3.23 (1.96-5.33)

*Adjusted for: Sex, Education, Income, Cohabitation status, Marital status, Divorce history, Smoking, and Physical exercise.
** Psychotic disorders, Anxiety disorders, Mood disorders, Personality disorders, Drug abuse.
†Other than: Psychotic disorders, Anxiety disorders, Mood disorders, Personality disorders, Drug abuse.
††: Psychotic disorders, Anxiety disorders, Mood disorders, Personality disorders, Drug abuse, and other psychiatric disorders.

Stratifying the study population according to psychiatric disorders other than AUD, showed that the risk of suicide among individuals with AUD was substantially different in the two sub-samples. As shown in Table 5, the risk of suicide was 2.21 (CI: 1.29-3.80) among people with psychiatric disorders while it was 9.69 (4.88-19.25) among people without psychiatric disorders when the reference group consists of individuals never registered with AUD.

Table 5. Hazard ratios (95% Confidence Interval) of completed suicide according to AUD, stratified by presence of psychiatric disorders. Reference group consist of individuals never registered with AUD.

	Registered with a psychiatric disorder (other than AUD)		**Never registered with a psychiatric disorder (other than AUD)**	
	Unadjusted	Adjusted for lifestyle covariates*	Unadjusted	Adjusted for lifestyle covariates*
Registered with AUD:	2.21 (1.29-3.80)	1.94 (1.08-3.49)	9.69 (4.88-19.25)	5.86 (2.83-12.15)

*Adjusted for: Sex, Education, Income, Cohabitation status, Marital status, Divorce history, Smoking, and Physical exercise.

6. DISCUSSION

In this section, the main findings are summarized, followed by discussions of some central issues of the thesis, and a discussion of the most important sources of bias. Focus will be on issues not discussed in the four papers; for further discussion, reference is therefore made to the papers.

6.1. Main findings

This thesis focuses on determinants, co-morbidity and consequences of AUD. The main findings are that:

- Amount and frequency of alcohol intake are associated with increased risk of AUD and there seems to be different thresholds in risks for men and women.
- Individuals who include wine when drinking alcohol have lower risks of developing AUD compared to individuals who do not include wine, independent of the total amount of alcohol consumed.
- Only a high weekly alcohol intake is associated with an increased risk of psychiatric disorders for women. For men, alcohol intake seems to have a protective effect of developing psychiatric disorders.
- AUD is frequently co-morbid with other psychiatric disorders. First-time AUD registration is most likely to precede first-time registration of mood disorders, psychotic disorders, anxiety disorders, personality disorders, and drug abuse in individuals with co-morbid AUD to their psychiatric disorder. The risk of developing a psychiatric disorder in individuals with AUD seems to be greater than the risk of developing AUD in individuals with other psychiatric disorders.
- Individuals with AUD are at an increased risk of committing suicide, and registered co-morbid psychiatric disorders are neither sufficient nor necessary causes in this association.

6.2. Usability of register-based research for studying alcohol use disorders

6.2.1. Berksonian bias

Associations between alcohol use disorders and their determinants, co-morbidity and consequences often derive from studying samples of treated or hospitalized patients. Because not all individuals with AUD are equally likely to be in these study samples, bias may result when findings are presumed to apply to the general population. This type of bias, known as Berksonian bias (131;132) (and often discussed in case-control studies) occurs whenever the association between the independent variable and the dependent variable differ between the general population and the population from which the sample derives (in this thesis: AUD in the general population and hospitalized or treated individuals with AUD). The magnitude of the potential bias consequent to Berksonian bias depends on the proportion and the selection of individuals with AUD who are treated and thereby registered. Most current studies indicate that the number of individuals with AUD who are in treatment is only a small proportion of individuals with AUD in the general population. The 1992 National Longitudinal Alcohol Epidemiologic Survey (133) estimated that over 27 million Americans have alcohol abuse or alcohol dependence, and at about the same time, it was estimated that only approximately 1.8 million Americans received treatment for alcohol problems (134). An American study based on data from the 2001-

2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), found that only 25.5% of people with alcohol dependence ever received treatment (135). In a Danish cohort survey performed in 2005, it was found by use of The Alcohol Use Disorder Test (AUDIT) that: 4.4% of the women and 12.2% of the men had a harmful alcohol intake, and that 1.0% of the women and 2.6% of the men were alcohol dependent (19), while we in CCHS found that, over a period of 26 years, 7.6% of the invited study population were registered at a hospital or at an outpatient clinic. All these estimates derive from different methodologies, and there are not any known estimates of the proportion of individuals with AUD in Denmark who is treated. However, it seems reasonable to assume that estimates drawn from registers, as it is the case in this thesis, only represent a certain percentage of individuals with AUD.

A recent study confirmed the presence of Berksonian bias with regard to investigating the association of the magnitude of alcohol use and a diagnosis of AUD (as studied in Paper I). They found that treated alcoholics are not simply former untreated alcoholics observed later in the progress of their disease, since non-treated alcohol dependent individuals generally came from a population with much lower alcohol use than treated alcoholics. They, thereby, rejected the hypothesis that non-treated alcoholics have similar alcohol use histories to treated alcoholics, but that they are just identified earlier in their drinking histories (136). The results suggest that it is not reasonable to generalize results from treatment samples of individuals with AUD to untreated individuals with regard to investigating previous alcohol intake. This means that findings of associations between AUD and determinants that may be predictive of differences in alcohol intake are also likely to be different in treated samples (such as register-based studies) and in the general population. And it also means that findings on the consequences of AUD that may be affected by differences in alcohol use (such as psychiatric co-morbidity or suicide) are not likely to apply to the general population.

A recent study investigated the presence of Berksonian bias according to psychiatric co-morbidity in individuals with AUD by comparing untreated versus treated individuals with AUD (137). They found that, compared to treated long-term abstinent individuals with AUD, active treatment-naïve individuals had fewer lifetime psychiatric diagnoses, a trend toward fewer current psychiatric diagnoses, fewer lifetime mood diagnoses, and fewer lifetime and current anxiety diagnoses. These results show that treated and untreated individuals with AUD are two different groups with regard to psychiatric co-morbidity, and they confirm the presence of Berksonian bias when generalizing register-based results of co-morbidity in individuals with AUD to individuals with AUD in the general population who are never treated. This underlines the importance of emphasizing that results from Paper III cannot necessarily be generalized to the general population.

6.2.2. Using b-MAST to assess validity of register-based AUD

In Denmark, the incidence of AUD can be assessed at different levels: The general population, patients at the general practitioner, patients in psychiatric hospitals, patients in somatic hospitals, and patients at outpatient clinics. In the present thesis, only the last three assessments were used to describe alcohol use disorders, and it can only be hypothesized how great a percentage of actual individuals with AUD that was detected using this categorization.

In CCHS-III, participants were asked to fill out the brief Michigan Alcoholism Screening Test (bMAST) (138), a ten-item version of the original MAST scale (5) that has been applied across a range of clinical and research settings (139-142). The b-MAST scores were calculated based on Pokorny et al. (138); with items weighted 0, 2, or 5; when summed, they yield scores ranging from 0 to 29. The majority of the items on the b-MAST refer to lifetime situations (e.g., "Have you ever been arrested for drunk driving or driving after drinking?"). Table 6 shows the distribution of individuals with and without registration with AUD on the bMAST scale using five groupings.

Table 6. Comparison of distribution of individuals with and without registered AUD on bMAST.

bMAST:	**Not registered with AUD (%) N= 9107**	**Registered with AUD (%) N= 469**	**Registered with AUD before CCHS-III (%) N= 333**	**Registered with AUD after CCHS-III (%)** N= 136
Mean (S.D.)	0.61 (1.89)*	8.66 (8.81)*	10.68 (9.18)	3.71 (5.20)
0-5	8903 (97.8)	237 (50.5)	131 (39.3)	106 (77.9)
6-11	147 (1.61)	52 (11.1)	40 (12.0)	12 (8.8)
12-17	39 (0.43)	89 (19.0)	75 (22.5)	14 (10.3)
18-25	17 (0.19)	76 (16.2)	72 (21.6)	4 (2.9)
26-29	1 (0.01)	15 (3.2)	15 (4.5)	0 (0.0)

* Mann-Whitney test comparing means of bMAST between the two groups: Registered with AUD/Not registered with AUD shows that $p<0.0001$.

Table 6 shows that the mean bMAST score is significantly higher among individuals registered with AUD (8.66) than among individuals who were never registered with AUD (0.61). Additionally; the mean bMAST score is higher in the group of individuals registered with AUD before answering the questionnaire of CCHS-III than in the group registered with AUD after answering the questionnaire.

Using bMAST as the golden standard of AUD, the **sensitivity of the registers used was 53.2%**, meaning that 53.2% of individuals with a B-MAST score of a minimum of 6 points are registered with AUD in the registers. The **specificity of the scale was 97.4%**, meaning that out of the individuals with a B-MAST score of 5 point or less, 97.4% are never registered with AUD.

Sensitivity and specificity in this study correspond well with previous studies (143;144) such as Chan et al. (145), who found sensitivity/specificity to be 48%/96% in the general population using heavy drinking instead of AUD.

The high specificity found in this study shows that, among respondents, most of the individuals who are not registered with AUD are correctly classified. Conversely, the sensitivity shows that the use of registers to assess AUD is subject to some uncertainty since only 53.2% of individuals with a B-MAST score of a minimum 6 points were registered with AUD in the registers. These results seem to indicate that register-based research of AUD is insufficient to detect all cases.

6.3. Using register-based research for studying psychiatric disorders

The advantage of assessing AUD and other psychiatric disorders from registers is the ease by which the study population can be followed continuously for various endpoints. However, register data can also induce several biases, especially misclassification. Misclassifications of psychiatric disorders and AUD mean that the sensitivity and/or specificity is less than 100 percent. Hence, misclassification of psychiatric disorders occurs, if for example individuals fulfilling criteria for an anxiety disorder were not diagnosed at a Danish hospital; or if individuals not fulfilling criteria for an anxiety disorder were diagnosed as such.

A recent Danish report concluded that if results from foreign studies are conveyed into Danish conditions – 20% of the population would each year have psychiatric symptoms corresponding to criteria for one or more psychiatric disorder (146). Hence it seems very likely that the sensitivity of psychiatric disorders in this thesis was not very high.

> In CCHS it was found that: 3724 (16.1%) of the invited study population and 2707 (14.9%) of the participants were registered with a psychiatric disorder (including AUD) during the 26 years of investigation.

If misclassification of AUD and other psychiatric disorders was differential in Paper III, meaning that individuals with co-morbid disorders were more likely to receive treatment than individuals with no co-morbid disorders, it would result in an overestimation of AUD co-morbidity rates among psychiatric patients and the presence of Berksonian bias, as described above.

Prevalence and co-morbidity rates of psychiatric disorders vary substantially among studies in the literature, primarily due to methodological issues and to large differences between clinical and population samples. Table 7 shows co-morbidity rates among individuals with AUD in the three different registers used in the thesis.

Table 7. Co-morbidity of psychiatric disorders with AUD in each register.

	WINALCO-database	**Danish Psychiatric Central Register**	**Danish Hospital Discharge Register**
Individuals with AUD:	**685**	**941**	**1024**
Number of individuals with AUD who has other psychiatric disorders:			
Mood disorders (%)	102 (14.9)	242 (25.7)	147 (14.4)
Psychotic disorders (%)	60 (8.8)	116 (12.3)	75 (7.3)
Anxiety disorders (%)	50 (7.3)	90 (9.6)	68 (6.6)
Personality disorders (%)	177 (25.8)	378 (40.2)	202 (19.7)
Drug abuse (%)	114 (16.6)	254 (27.0)	160 (15.6)
Any psychiatric disorder (%)	328(47.9)	702 (74.6))	480 (46.9)

Table 7 shows that the co-morbidity rate is highest in the psychiatric register, hence, 74.6% of individuals registered with AUD in the Psychiatric Register is also registered with another psychiatric disorder in one of the three registers. The rates of co-morbidity are higher for all categories of psychiatric disorders in the Psychiatric Register compared to the Winalco database and the Hospital Discharge Register; in these two registers the rates are very alike.

It can be argued that co-morbidity rates in Papers III and IV are intermediate between: population studies screening for psychiatric disorders, and clinical studies examining hospitalized patients. The first type of study would most likely find lower co-morbidity rates than the present study, while the second type would most likely find higher co-morbidity rates. The reason why co-morbidity rates from this thesis are more likely to be lower than clinical studies is that AUD in this thesis is defined based on three different registers, two of which have a lower co-morbidity rate than the Psychiatric register. In addition, some clinical studies are based on individuals with a severe degree of AUD, in which case a higher co-morbidity rate is to be expected.

The use of registers means than the study relies on clinicians at the somatic – and psychiatric hospitals for diagnosis, meaning that standardized diagnostic measures were not utilized. In addition, as the definition of AUD in this thesis originates from the merging of three different registers, there are further risks of differences in diagnostic practice since registration practices might have been different in the different settings. Also, the diagnostic practice in the Danish Hospital Discharge Register changed in the year 1995: Before, ambulatory care was not included in the registers whereas after, all ambulatory care was included. Hence, disorders treated in ambulatory care before 1995 are not registered and there is a possibility that these disorders may be underreported. In addition, information on ICD-8 diagnoses was collected prior to 1994, whereas ICD-10 diagnoses were collected after 1994, and since there are differences between the two classification systems, comparisons across classifications could yield bias according to preference of clinicians to use certain diagnoses. The size of the bias related to these possible dissimilarities in diagnostic practice is unknown and, as far as it is known, no studies have investigated this.

Patients may be affected by psychiatric disorders for longer or shorter periods before they are admitted, so in addition to possible differences in diagnostic practice, register-based research in psychiatric disorders is also subject to the potential noise and bias that this period may inflict. Hence, the time of onset of each psychiatric disorder is based on the time when the individual appeared in the registry, although in some cases it is likely that the disorder developed months or years before the individual entered treatment. As a consequence, it is especially difficult to make interpretations on the temporal ordering of the disorders.

6.4. Alcohol intake and psychiatric disorders

According to the results from Paper I and the sub-study on alcohol intake and psychiatric disorders, the effects of the amount of alcohol intake seems to be dissimilar according to the risk of AUD and to the risk of other psychiatric disorders. The risk of AUD increased dose-dependently with increased alcohol intake, and, conversely, the risk of other psychiatric disorders did not appear to increase with increased alcohol since only a large

weekly intake of alcohol showed a tendency towards an increased risk of psychiatric disorders for women; for men there even seemed to be a protective effect of drinking alcohol. Hence, although the psychiatric co-morbidity of AUD is very high, alcohol intake does not seem to be a common risk factor of both AUD and other psychiatric disorders.

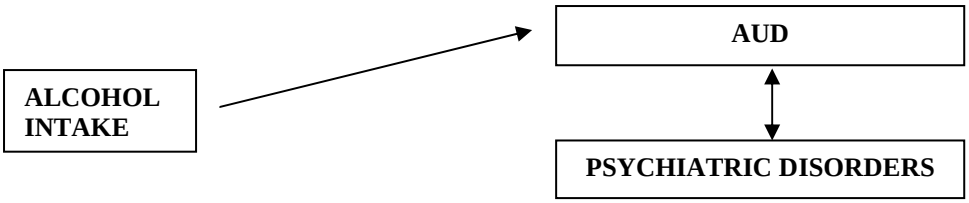


Figure 10 shows the distribution of the amount of alcohol intake in CCHS-I, exemplifying how a relatively large percentage of the study population (13.8%) drinks above 21 drinks of alcohol per week.

Figure 10. The amount of alcohol intake among participants in CCHS-I.

The Danish National Board of Health's sensible drinking limits of 14 and 21 drinks per week are primarily set up based on the risk of alcohol-related physical diseases and mortality. But whereas 14 and 21 drinks per week is a large amount of alcohol in relation to the physical influences of alcohol on the body – it may not be very much according to psychological and social effects. The limits correspond to 2-3 drinks per day (if the intake is spread out over the week) – intakes that according to the results from this thesis does not seem to be sufficient to increase the risk of psychiatric disorders.

Other studies have investigated the association between alcohol intake and psychiatric disorders; this has especially been the case for depression. A positive association between alcohol consumption and depression has been found in a number of studies (91-94), with several studies finding different results according to the measures of alcohol consumption used (95-98). In one study, a U-shaped relationship between alcohol consumption and depression has been showed where abstainers were at greater risk of depressive symptoms than those who drink modestly (99).

The pattern of a U-shaped relationship between alcohol intake and psychiatric disorders was found among men for all psychiatric disorders. This apparently protective effect of alcohol for men indicates that alcohol consumption among men is a sign of mental and social well-being and normal functioning. In Paper I, Table 1, the descriptive characteristic

of different categories of drinkers shows that, compared to all other groups of drinkers, non-drinkers are more likely to: Be women, have a short education, have a low income, be non-smokers, do little physical activity, to live alone, to not be currently married, and to be a widow. Hence, non-drinking may be an indicator of suboptimal mental and social functioning and therefore might be associated with a higher risk of psychiatric disorders. Another explanation could be that alcohol to some extent acts as an alternative psychoactive medication among men wherefore alcohol consumption is associated with a lower risk of psychiatric disorders.

Whereas there for men seemed to be a protective effect of drinking some alcohol, women in this study did not seem to have a protective effect of drinking. Instead, women increased their risk of psychiatric disorders with high weekly intakes of alcohol. This increased risk could be due to alcohol-related problems such as the depressive effects of alcohol (147;148) and the psychosocial consequences of problem drinking, or the estimates could be due to the fact that women with psychiatric problems self-medicate their symptoms with alcohol. One study showed that self-medication with alcohol is a common behaviour in individuals with anxiety disorders (measured by interview) and that those individuals are at increased risk of mood and substance use disorders (149).

Only for women, the risk of psychiatric disorders increased with a large alcohol intake – and even for intakes over 21 units per week, the risk only increased slightly. Except from the explanation that alcohol simply does not affect the risk of developing a psychiatric disorder significantly, there are several other explanations as to why we in this study find alcohol intake and psychiatric disorders to only be associated to some extent. Moderate alcohol use could, in these days, be thought to be an expression of general lifestyle behaviour and not be a specific coping response to psychological problems. In addition, an obvious explanation for the results could be that there is selection bias in this study, since individuals with AUD and individuals with other psychiatric disorders were less likely to participate (see Table 9).

Looking at alcohol intake as a risk factor, individuals with psychiatric disorders may be divided into two groups: *One group* of individuals with psychiatric disorders who have previously been registered with AUD or have co-morbid AUD to their psychiatric disorder, and a *second group* of individuals with psychiatric disorders who never had AUD. In the fist group, individuals would most likely have had a large alcohol intake, wherefore the association between alcohol and psychiatric disorders would appear to be significant. In the second group, however, alcohol would not seem to affect the risk of psychiatric disorders other than AUD. If these two groups diverge according to alcohol intake as a risk factor, it is plausible that other risk factors also could be different for these two groups.

The main conclusion from this study is that in this particular study population, CCHS I-III, the majority of individuals could consume more than recommended amounts of alcohol without increasing their risk a psychiatric disorder. However, since this study is register-based, the results should be interpreted with caution, and other studies should be done to evaluate this association. Nevertheless, if it is a fact that alcohol is not generally a risk factor for psychiatric disorders, but only for AUD, the aetiology of AUD and other

psychiatric disorders is obviously not very similar, and this may be of interest to general practitioners as well as to researchers who investigate psychiatric co-morbidity.

6.5. The impact of using non-drinkers as a reference group in Papers I and II

Non-drinkers were used as reference group in Papers I and II . Hence, all hazard ratios are expressions of the increased risk compared to non-drinkers. In many high-income countries, such as Denmark, alcohol consumption is the norm rather than a deviation since the majority of the population drink alcohol. And using non-drinkers as a reference group in epidemiological studies has been criticized due to the fact that this group has shown to differ from drinkers in terms of other health determinants (150) and that results based on non-drinkers as the reference group therefore may be more prone to potential confounding. Also, the hypothesis of "sick-quitter" has been proposed: That people stop consuming alcohol due to health problems (151), thereby making non-drinkers a group that differ from the normal population.

Using non-drinkers as a reference group has also been criticized due to the heterogeneity of non-drinkers, as there are at least two distinct groups of non-drinkers: 1) Individuals who never drank alcohol and 2) Individuals who previously drank large amounts of alcohol and now are abstinent. The health outcomes for these groups have shown to be different – for example according to mortality where former drinkers were found to have a higher mortality risk than lifetime abstainers (152). If the risk of AUD is different in the two groups it would be an advantage to separate them in order to constitute a more homogeneous comparison group.

To evaluate the composition of the non-drinking group, information from CCHS-III was used, since only respondents in CCHS-III were asked whether their alcohol intake changed during the past 10 years:

> Among the 2022 non-drinkers in CCHS-III who answered the question about previous alcohol intake; 220 (11%) reported that they previously drank considerably more than they drink now. 1789 (89%) reported to have been drinking either less (7%) or the same amount of alcohol (93%) as they drink now, and only 32 (1.8%) in this group had been registered with AUD at some point. This suggests that the main proportion of non-drinkers is people who have never been drinking alcohol – at least not within the past 10 years.

A recent study used a baseline and two follow-up studies to evaluate measurement error of alcohol intake and found that 52.9% of those who in the last follow-up reported never having a drink of any alcoholic beverage reported drinking in previous surveys. The study did, however; also find that most of the drinking reported previously was of low frequency and low quantity, wherefore the resulting measurement error for establishing risk was minor (153).

Additional analyses in Papers I and II, where the reference group was changed from non-drinkers to individuals who drink 1-7 or 1-6 drinks of alcohol per week, showed that: The sex-differences in HRs were diminished in Paper I, as the risks for men and women

became almost identical except for very high intakes of more than 41 drinks per week. Also in Paper II, the hazard ratios for men and women respectively approached. For example, the HRs among non-wine drinkers who drink more than 21 drinks per week was 4.3 (95% CI: 1.9-9.5) and 4.9 (95% CI: 2.9-8.3) for men and women, respectively, which is a noticeable change in the differences in estimates compared to the results in Paper II, where the reference group is non-drinkers. It thus seems that the sex-differences found in Papers I and II depend upon the reference group that was used. The reasons for this could be that non-drinking women and non-drinking men are not comparable groups according to other health determinants in the same way that women and men drinking up to 6 or 7 drinks per week are comparable groups. In addition, the results in Paper I are based only on data from CCHS-I and thereby alcohol intake in 1976-78, and there is a possibility that non-drinking at that time had different reasons and implications among men and women than it has today.

The above-mentioned sections discuss potential biases related to using non-drinkers as the reference group. And especially the differences in results in Papers I and II according to reference group raises the question of which group that should optimally be used. However, choosing the right reference group should not only be based on potential problems there might be, but also on considerations of which reference group that is most relevant to use according to the research questions in focus. The group with the lowest risk of AUD would undoubtedly be consisting of individuals who do not drink alcohol at the time of investigation and using this group as reference shows the effects of alcohol compared to abstinence. If however, the purpose had been to investigate risk of AUD within the population of drinkers, the group of individuals drinking some alcohol every week should have been used as the reference group.

6.6. Main sources of bias

6.6.1. Misclassification

Misclassification of exposure and/or endpoints in a cohort study is inevitable, most likely also in the present thesis where the various exposures and endpoints presumably have been subject to some misclassification. The following discusses the most important aspects of this bias.

Alcohol intake

Differential misclassification where persons with and without AUD misreport to different extents were minimized due to the fact that information on alcohol was collected prospectively. While the validity of questionnaire information on drinking frequency has not been examined, the reliability of self-reported amount of alcohol intake was investigated in other studies using the same alcohol questions as in the present study, and close agreements between questionnaire information and dietary interview were found (154). Self-reports of alcohol have, however, also been found to be biased towards an underestimation among the heaviest drinkers (155). The level of high-density lipoprotein cholesterol in the blood has been suggested as a biochemical marker of alcohol intake (156;157), and in CCHS, Johansen et al. have observed a dose-response relation between alcohol intake and high-density lipoprotein cholesterol (158). If systematic underreporting of alcohol consumption has occurred in Papers I and II, the results showing the risks of AUD are overestimated, and if non-differential misclassification has occurred the estimates are in most cases believed to be underestimated (159). However, based on the

above-mentioned studies on validity it seems that in this thesis alcohol intake was generally measured in a valid manner and that misclassification of alcohol intake was not an important aspect.

A possible source of misclassification in Paper II is the weekly amount of each beverage type. The questionnaire information used does not contain information on alcohol content, hence there is no distinction between for example light and strong beer. If heavy drinkers generally drink beer, wine, and spirits with a higher percentage of alcohol than do light and moderate drinkers this would lead to an underrated association between type of alcohol and AUD. This particular misclassification have not been investigated, however, Grønbæk et al. found that beverage specific alcohol reporting bias seemed to be non-differential (154).

Follow-up

A long follow-up time was used in this thesis, which is usually considered to be a strength in prospective studies. With regard to misclassification, however, this prolonged follow-up time may be problematic, especially in Papers I and II where exposure is measured by questionnaire information. Many studies have only a base-line measurement of exposure and then an outcome measurement several years later, with the exposure assumed to be stable during this time. With regard alcohol intake, however, there is especially the probability of changes in alcohol intake with increased follow-up time, leading to an increased risk of misclassification of exposure. Using repeated measures on alcohol intake during follow-up, as was done in Paper II, could reduce this possible misclassification caused by changes in alcohol habits. And due to the use of this study design, misclassification of alcohol intake is believed to be considerably reduced in this paper. It can, however, be discussed whether it is best to use one baseline measure of alcohol, or whether it is best to use updated measures since this would depend on the outcome of interest. Studies of alcohol intake and cancer have found dissimilar results according to different cancer forms in term of whether baseline intake or repeated exposure information is the best predictor (124), and according to cardiovascular disease and mortality it has been suggested that – baseline measures of alcohol intake is not adequate. However, according to AUD the optimal method is not known.

Suicide

Underestimation of the prevalence of completed suicides was likely in Paper IV. The diagnoses used to capture completed suicide were all in the subcategories of "Suicide and self-inflicted injury" (ICD-8) or "Intentional self-harm" (ICD-10). However, diagnoses of "Injury undetermined whether accidentally or purposely inflicted" (ICD-8: E980-989), "Event of undetermined intent" (ICD-10): Y10-Y34), "Poisoning accidents" (ICD-8: E861-877), and "Poisoning" (ICD-10: (T36-50, T52-60) were not defined as completed suicides in the study. The boundary between completed suicide and accidental death could have been complex to determine in some cases, and practitioners in doubt would most likely have registered these causes of death as accidental. Therefore, cases were possibly lost that were wrongly diagnosed in these subcategories. Table 8 shows the prevalences of causes of death in the above-mentioned categories.

Table 8. Prevalence of possible misclassification of completed suicide among invited individuals for CCHSI-III.

	Number of persons registered using ICD-8	Number of persons registered using ICD-10
"Injury undetermined whether accidentally" or "Purposely inflicted" (E980-989) **or "Event of undetermined intent"** (Y10-34)	71	11
"Poisoning accidents" (E861-877) **or "Poisoning"** (T36-50, T52-60)	23	21

Table 8 shows that the diagnosis of "Injury undetermined whether accidentally or purposely inflicted" in ICD-8 had most registrations. Taking into account the overlap of diagnoses, a total of 119 deaths were classified within the diagnoses in Table 8 – suggesting that the possible misclassification of completed suicide was not substantial. It is, however, most likely that misclassification was present to some degree, and this would most likely lead to underestimation of the significance of the findings in Paper IV.

6.6.2. Selection bias

Selection bias is a systematic error where the relation between the independent and dependent variable is different for those who participate and for those who are eligible for the study but do not participate. In the prospective study used, selection bias would occur if individuals who did not participate were different from participants. Berksonian bias is one type of selection bias already described above. There are, however, several ways in which non-participants in this thesis could have been different from participants. Considering CCHS-I-III, 23,189 individuals were invited and 18,146 participated in at least one of the rounds. Among the 5,043 individuals who did not participate in any of the rounds, information on AUD, psychiatric disorders and suicide was available through Danish registers; results are shown in Table 9.

Table 9. Differences between respondents and non-respondents in CCHS-I-III according to AUD, psychiatric disorders, and suicide:

	Participants (%)	Non-participants (%)	Chi-square test sig.
AUD	1200 (6.6)	556 (11.0)	<0.0001
Psychiatric disorder	2092 (11.5)	760 (15.1)	<0.0001
Suicide	123 (0.68)	86 (1.71)	<0.0001

As shown in Table 9, there are significant differences between participants and non-participants in CCHS-I-III, as incidences of AUD, psychiatric disorders, and suicide were higher among non-participants compared to participants. Other studies have shown that non-participation in CCHS was associated with lower income, higher mortality, and lung cancer (124), and higher incidence of AUD and alcoholic liver cirrhosis (160). In other study populations it was found that non-participants are more likely to be unmarried (161), have a shorter education and lower socioeconomic status (161;162), to smoke (161),

and to have higher morbidity (163;164) and mortality (165). In the present thesis it was not possible to investigate drinking habits in non-respondents, and for this reason the size of selection bias in Papers I and II is not known. It was, however, investigated in two studies from The Netherlands: one found an overrepresentation of non-response among abstainers (166), and one found that non-respondents do not generally drink more than respondents and that female non-respondents generally drink less (167). As both exposure and outcome in Papers III-IV are associated with participation in the study (Table 9) – the internal validity in these studies may be affected by selection bias.

6.6.3. Confounding

In CCHS there is information on various health and lifestyle related risk factors. There is, however, still the possibility of residual confounding or confounding due to unmeasured covariates and this could affect the interpretation of the results in the thesis.

In Papers I and II, the associations between amount, frequency, and type of alcohol intake and AUD could possibly be biased by confounding factors such as: intelligence (168), personal characteristics (42;43;45;46;85;88;169), diet (89;170), disease symptoms (90), quality of life (83), and drinking patterns (171;172). In addition, income and education (each divided into three groups) were used as proxy to social class, and these may be considered rough measures of a factor that could be an important confounder.

For a covariate like co-morbidity it may be difficult to decide whether is should be considered a confounder or a mediator, and this must be based on theoretical considerations. In Paper III, it could be argued that analyses investigating associations of AUD with each single group of psychiatric disorders should include other psychiatric disorders as possible confounding factors to account for the fact that psychiatric disorders are highly co-morbid with one another as well as with AUD. For co-morbidity to be a confounding factor in Paper III, the co-morbidity should not be a consequence of the exposure (AUD or another psychiatric disorder) and, thereby, not be a mediator. This, however, was not considered plausible since the co-morbid psychiatric disorder would often be a mediator, for which reason it was decided not to adjust for co-morbidity. Another argument for not adjusting for co-morbidity is that the sample size would make it impossible to perform a detailed adjustment. Having AUD and a co-morbid psychiatric disorder is obviously an indication of susceptibility to psychiatric disease, and possible confounding factors in these co-morbid associations would presumably be genetic factors together with personality factors. Unfortunately it was not possible to adjust for such factors.

In Paper IV, adjustments were made according to sex, education, income, cohabitation status, marital status, divorce history, smoking, and physical exercise. It is, however, not unlikely that AUD and suicide are manifestations of some common underlying traits that were unmeasured in this study. Such factors could be: Aggression, impulsivity and hopelessness (115), and abnormal serotonergic function (173-175).

6.6.4. Loss to follow-up

In CCHS, less than one percent of participants were lost during follow-up. Due to the unique personal identification number, all outcome measures, except those for participants who were hospitalized in other countries, could be followed using Danish registries. Such

minor loss to follow-up is not believed to have affected the results obtained in any of the papers.

6.7. Generalizability over time

As it is the situation in all epidemiological studies with a long follow-up time, there was in this thesis the possibility of period effects; especially in Paper I and II which investigates alcohol intake as a determinant of AUD. The results found in Paper I are based on information on alcohol intake in 1976-78, while the results in Paper II are based on information on alcohol intake between 1976-1994. The contexts in which alcohol is being consumed have most likely changed along the past decades, whereby there is also the possibility that the associations between alcohol intake and other health determinants have changed. This would affect the associations between alcohol intake and health consequences and among these AUD. It can therefore be discussed whether the results can be generalized to the generations of the 21st century and only new studies using newer data would be able to illuminate this.

7. CONCLUSIONS AND PERSPECTIVES

7.1. Conclusion

This thesis showed that the risk of AUD increased dose-dependently with increased amount and frequency of weekly alcohol intake, and when the reference group was non-drinkers, the thresholds of significance was very different for men and women. Individuals who include wine as part of their alcohol intake had a lower risk of AUD compared to individuals who do not include wine, irrespective of the total amount of alcohol consumed – this was *not* considered to be due to specific ingredients in different types of alcohol, but rather to be an expression of confounding factors that were not assessable in the study. While the risk of AUD increased dose-dependently with increased alcohol intake, only a relatively high weekly alcohol intake was associated with the risk of psychiatric disorders for women while there for men seemed to be a protective effect of drinking alcohol according to psychiatric disorders. The psychiatric co-morbidity of AUD was investigated, and among registered individuals, the psychiatric co-morbidity with AUD was frequent, and AUD was registered before the co-morbid psychiatric disorder more often than the reverse temporal order. In addition, the risk of developing a psychiatric disorder in individuals with AUD seemed to be greater than the risk of developing AUD in individuals with other psychiatric disorders. AUD increased the risk of suicide, and it was concluded that registered co-morbid psychiatric disorders are neither sufficient nor necessary causes in this association.

Examining various sources of bias gave no reason to believe that each bias separately is likely to have affected the conclusions of the results. It is, however, important to note that all conclusions in the thesis are based on register information, and for this reason the generalizability and applicability of the results to the entire population could be limited.

7.2. Public health implications

Other studies have shown that overall alcohol intake is a good predictor of alcohol-related harm (66-70), and that different types of alcoholic beverages have different health-related outcomes (72-79;83;176;177). It has, however, to the authors' knowledge, not previously been explored how amount, frequency, and type of alcohol are associated with the risk of developing AUD. Danish, and several other international sensible drinking limits for alcohol intake, are 14 and 21 drinks for women and men, respectively. With regards to AUD, this thesis confirms the fact that for men this limit may be relevant, whereas for women the limit seems to be too high. However, the sensible drinking limits are established based on global measures such as overall morbidity and mortality, and AUD is only a small part of this. The beneficial effects of wine in relation to AUD were not investigated in other studies, and more research is needed to investigate the reasons for this beneficial effect, before recommendations should be made in this area.

The observed substantial co-morbidity between AUD and other psychiatric disorders underlines the need for ongoing development of improved treatments for those individuals meeting the criteria for both AUD and other psychiatric disorders; especially due to research showing that patients with co-morbid AUD often have a *poorer* treatment response and a *worse* course of illness over time than do individuals with no co-morbidities (104;108-111). Although we found that the risk of a psychiatric disorder for

individuals with AUD is larger than the risk of AUD for individuals with psychiatric disorders, it is difficult, based on register data, to make conclusions regarding temporal ordering in an etiological perspective. It is, however, reasonable to assume that the temporal order of AUD and other psychiatric disorders has important implications for treatment (178-180), and consequently it would be of great importance to evaluate the temporal ordering of these disorders in other studies.

Evidence linking AUD and suicidal behaviour has been reported in the literature for several decades (114-117). However, our results showing that AUD is associated with an increased risk of suicide irrespective of the presence of other psychiatric disorders have not been found in other studies. These results emphasize the importance for professionals to treat AUD and to be especially aware of potential suicide ideation in this population – irrespective of the presence of other visible psychiatric disorders.

AUD is very prevalent in many countries wherefore even a relatively small change in risk could have a large public health impact at the population level. The large population of individuals with AUD in addition to the high frequency of co-morbid psychiatric disorders and suicide combined with the damaging effects on individuals, families, and society make AUD a disorder that would greatly benefit from more research.

7.3. Future research

Both epidemiological and biological studies have tried to elucidate the nature of AUD – but there is still much to be unravelled. This thesis has investigated a few well-defined aspects of determinants, co-morbidity and consequences of AUD, and the conclusions from these studies have resulted in new and partly unexpected findings. However, AUD was in this thesis defined by using register-information and this measure did probably not fully capture all cases of AUD. In order to get a more accurate assessment of AUD and the relation to previous alcohol intake, psychiatric co-morbidity, and suicide, future studies should ideally include personal interviews to capture individuals with AUD. In addition the studies should ideally be prospective in design, with a large number of follow-ups in order for AUD to be recorded at the time of origin, and they should be large enough to ensure sufficient statistical power. According to the co-morbidity of AUD and other psychiatric disorders, future studies should also, in addition to including personal interviews to capture AUD, include personal interviews in order to capture *other* psychiatric disorders. This would especially be important in studies trying to illuminate the causality of the disorders.

The results from Paper II indicated that risk factors of developing AUD may be related to aspects that were not measured in CCHS. Examples of such aspects could be personality traits such as aggression, impulsivity and hopelessness (115), social anxiety disorder (41), sensation seeking behaviour (42;43), seasonal affective disorder (44), the personality trait of novelty seeking (45), and sense of coherence (46). This thesis mainly focused on common lifestyle factors as confounding factors, but in future studies it may be of interest to measure aspects of personality traits.

This thesis has focused on a study population with ages ranging from 20 to 93 at baseline, and with a follow-up time of 26 years. In future studies it may be of interest to investigate the relation of AUD with alcohol intake, psychiatric co-morbidity, and suicide in a

different study population that follows participants from a very young age. This should include information on exposures and outcomes at frequent time-points in life and address the research aims in a life course perspective. Alternatively, intervention studies could be done where participants with AUD were randomized either to intervention with the aim of treating the symptoms of AUD and lowering the alcohol intake or to a control group. The two groups could then be followed to investigate psychiatric disorders and suicide in each group. Such a study would give more knowledge of the dynamics between AUD and other psychiatric disorders and suicide. It would, however, require thorough ethical considerations and permissions, and depending of the length of treatment and follow-up, there would be large expenses.

SUMMARY IN ENGLISH

Alcohol-use disorders (AUD) are recognised and classified as mental disorders, with AUD consisting of the conditions of *harmful use of alcohol* and *alcohol dependence*. AUD is among the most prevalent psychiatric disorders in the general population, and individuals with AUD often have co-morbid psychiatric disorders, contributing to the increased risk of both morbidity and mortality.

The main purposes of this thesis were to:

1) Analyze the association between amount and frequency of alcohol intake and the later risk of AUD.
2) Examine whether preferred type of alcoholic beverage influences the later risk of AUD.
3) Analyze the association between amount of alcohol intake and the later risk of psychiatric disorders.
4) Investigate psychiatric co-morbidity and temporal ordering of AUD and other psychiatric disorders.
5) To analyze the risk of suicide among individuals with AUD and to assess the role of other psychiatric disorders in this association.

The results obtained are presented in four scientific papers, all of which are either published or in press; the fifth is under preparation for publication.

This thesis is based on the Copenhagen City Heart Study (CCHS), which is an ongoing series of studies conducted in the Danish population from 1976 and onwards. All participants were followed by use of the unique personal identification number with linkage to Danish registers: The Danish Hospital Discharge Register, the Danish Psychiatric Central Register, the WINALCO-database, and the Danish Causes of Death Register. The main statistical analysis used was Cox proportional hazard regression.

In the first paper, we found that amount and frequency of alcohol intake were significantly associated with an increased risk of AUD. With the reference group being non-drinkers, the thresholds of significance were very different for men and women, since women significantly increased their risk by drinking 1-7 drinks per week, whereas the risk for men showed no significant increase before weekly intakes of alcohol of more than 21 drinks per week.

In the second paper, we found that individuals who drink wine as part of their alcohol intake have a lower risk of AUD compared to individuals who do not include wine, irrespective of the total amount of alcohol consumed. We concluded that the findings were most likely to have appeared due to confounding factors that were not assessable in the study, rather than to specific ingredients in different types of alcohol.

In the sub-study of alcohol intake and risk of psychiatric disorders, we found that if the reference group was non-drinkers; women were at increased risk of psychiatric disorders only if they drank more than 14 drinks per week. For men, there was no increased risk of

any psychiatric disorder with high intakes of alcohol. Conversely, drinking alcohol every week seemed to have a protective effect towards psychiatric disorders in men.

In the third paper, we concluded that AUD is frequently co-morbid with other psychiatric disorders. First-time AUD registration was most likely to *precede* first-time registration of psychiatric disorders, such as mood disorders, psychotic disorders, anxiety disorders, personality disorders, and drug abuse. And the risk of developing a psychiatric disorder in individuals with AUD seemed to be *greater* than the risk of developing AUD in individuals with other psychiatric disorders.

In the fourth paper, we found that individuals with AUD are at increased risk of committing suicide, and that registered co-morbid psychiatric disorders were neither sufficient nor necessary causes in this association. The findings may however be a result of the fact that analyses are based on register information wherefore generalizability of the results may be limited and not applicable to the general population.

Based on register-data, a prevalence of AUD of 7.6% was found among the invited study population in CCHS I-III. This, in addition to the observed substantial psychiatric co-morbidity with AUD, emphasises the need for ongoing development of improved treatments for individuals meeting the criteria for both AUD and other psychiatric disorders; especially because previous research shows that patients with co-morbid AUD often have a *poorer* treatment response and a *worse* course of illness over time than do individuals with no co-morbidities. In addition, the increased risk of suicide among individuals with AUD proven in this thesis underlines the importance of treating AUD and to be especially aware of potential suicide ideation in this population – irrespective of the presence of other visible psychiatric disorders.

RESUMÉ PÅ DANSK

Alkoholisme defineres som en psykisk sygdom og er generelt en sammensætning af betegnelserne alkoholmisbrug og alkoholafhængighed. Alkoholisme er blandt de mest udbredte psykiske sygdomme i befolkningen, og personer med alkoholisme har ofte andre psykiske sygdomme, som bidrager yderligere til den øgede risiko for både sygdom og død, som i forvejen findes blandt alkoholikere.

Hovedformålene med denne afhandling var at:

1) Analysere sammenhængen mellem mængden og frekvensen af alkoholindtag og risikoen for at udvikle alkoholisme.
2) Undersøge om forskellige typer af alkohol indvirker forskelligt på den senere risiko for at udvikle alkoholisme.
3) Analysere sammenhængen mellem mængden af alkoholindtag og risikoen for at udvikle en række psykiske sygdomme.
4) Undersøge ko-morbiditet og tidsmæssig sekvens af alkoholisme og andre psykiske sygdomme.
5) Analysere risikoen for selvmord blandt personer med alkoholisme, samt undersøge hvilken betydning andre psykiske sygdomme har for denne sammenhæng.

De opnåede resultater er præsenteret i fire videnskabelige artikler, som alle enten er publicerede eller "in press", mens den femte er under forberedelse til publicering.

Afhandlingen er baseret på Østerbro-undersøgelsen (CCHS) som er en igangværende serie af studier udført i den danske befolkning siden 1976 og frem. Alle inviterede er fulgt ved hjælp af CPR-nummeret og linket til de danske registre: Landspatientregistret, det Psykiatriske Centralregister, WINALCO-databasen, og Dødsårsagsregistret. Størsteparten af de statistiske analyser er udført ved *Cox proportional hazard regression*.

I den første artikel fandt vi, at både mængde og frekvens af alkoholindtag var signifikant associeret med en øget risiko for alkoholisme. Når referencegruppen var personer som ikke drak, var tærskelværdien for øget risiko for alkoholisme meget forskellig for mænd og kvinder. Således øgede kvinder deres risiko signifikant ved indtag af 1-7 genstande om ugen, mens mænd først øgede deres risiko signifikant ved indtag af over 21 genstande om ugen.

I den anden artikel fandt vi, at personer, hvis alkoholforbrug inkluderede vin, havde lavere risiko for alkoholisme sammenlignet med personer som ikke inkluderede vin, uanset mængden af det ugentlige alkoholindtag. Vi konkluderede, at resultaterne højst sandsynligt skyldes konfoundere, som det ikke var muligt at justere for, snarere end de skyldes forskellige ingredienser i forskellige typer af alkohol.

I sub-studiet om alkoholindtag og risiko for alkoholisme fandt vi, at hvis referencegruppen var personer som ikke drak, så havde kvinder, der drak over 14 genstande om ugen, en forøget risiko for psykiske sygdomme. For mænd var der ingen forøget risiko for psykisk sygdom selv ved store ugentlige indtag af alkohol; det så tværtimod ud til at der var en beskyttende effekt af at drikke alkohol hver uge.

I den tredje artikel konkluderede vi, at alkoholisme er en diagnose, som ofte er ko-morbid med andre psykiske sygdomme. Hos personer med ko-morbid alkoholisme var førstegangsregistrering med alkoholisme oftest registreret *før* førstegangsregistrering af affektive lidelser, psykotiske lidelser, angstlidelser, personlighedsforstyrrelser, og stofmisbrug. Og risikoen for at udvikle en psykisk sygdom hos personer med alkoholisme så ud til at være *større* end risikoen for at udvikle alkoholisme hos personer med en psykisk sygdom.

I den fjerde artikel fandt vi, at personer med alkoholisme er i øget risiko for at begå selvmord, og at andre registrerede psykiske sygdomme hverken er tilstrækkelige, eller nødvendige, faktorer i denne sammenhæng. Resultaterne kan dog skyldes det faktum, at analyserne er baseret på registerforskning, hvorfor man bør være varsom med at generalisere resultaterne til den generelle befolkning.

Blandt alle inviterede til Østerbro-undersøgelsens tre første runder fandt vi en prævalens af alkoholisme på 7,6%. Dette, samt det faktum at vi fandt en betragtelig psykiatrisk ko-morbiditet blandt personer med alkoholisme, understreger betydningen af fortsat fremgang og udvikling i behandling af personer med ko-morbid alkoholisme. Ikke mindst grundet tidligere forskning, som har vist, at personer med ko-morbid alkoholisme ofte har *dårligere* virkning af behandlingen og *dårligere* sygdomsudvikling over tid end personer som ikke har andre psykiske sygdomme udover alkoholisme. Den øgede risiko for selvmord blandt personer med alkoholisme, som blev fundet i denne afhandling, understeger desuden vigtigheden af at behandle alkoholisme samt at være særligt opmærksom selvmordsrisiko i denne befolkningsgruppe – uanset tilstedeværelsen af andre psykiske sygdomme.

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Paper I

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AMOUNT OF ALCOHOL CONSUMPTION AND RISK OF DEVELOPING ALCOHOLISM IN MEN AND WOMEN

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Abstract — Aims: It is generally accepted, but not yet documented that the risk of future alcoholism increases with the amount of alcohol consumed. The objective of this study was to investigate this association using the Copenhagen City Heart Study. **Methods:** Quantity and frequency of alcohol intake was measured in 19 698 men and women randomly drawn from the Copenhagen Population Register in 1976–78. The study population was linked to three different registers in order to detect alcoholism, and average follow-up time was 25 years. **Results:** After adjustment for all putative confounders, the risk of alcoholism for women increased significantly at 1–7 drinks per week with a hazard ratio (HR) of 2.02 (95% confidence interval (CI): 1.16, 3.53) compared to never/almost never drinking; the HR for drinking monthly was 1.75 (95% CI: 1.08, 2.85). The risk for men did not increase significantly before 22–41 drinks per week (HR = 3.81, 95 % CI: 2.18, 6.68) or if they had a daily alcohol intake (HR = 3.55, 95 % CI: 2.11, 5.99). Smoking was independently associated with the risk of alcoholism for both men and women. **Conclusion:** The risk of developing alcoholism increased significantly by very low intakes of alcohol in women, while the risk is only increased significantly in men consuming more than 21 drinks per week.

INTRODUCTION

Alcohol is one of the leading risk factors and is responsible for 4% of the global disease burden (World Health Organization, 2002). Moreover, harmful drinking is associated with increased risk of developing alcoholism, often leading to social, financial and interpersonal losses, stigmatization and social marginalization (Poznyak *et al*., 2005). Several studies have demonstrated that *both* genetic and environmental factors are involved in the development of alcoholism, but the complex interactions between genotype and environment have made it difficult to identify individual determinants of alcoholism. In 2002 a meta-analysis was performed including 50 family—twin—and adoption-studies in which problem drinking and alcohol dependence served as the primary outcome measures. The results indicated an upper limit of 20–26% for the heritability of alcohol misuse, which is a fairly lower than the rate often cited in the literature (Walters, 2002). Individual characteristics such as devotion and conservatism (Kendler *et al*., 1997), have been shown to be inversely associated with alcoholism while factors such as sensation seeking behaviour (Kampov-Polevoy *et al*., 2004; Lejoyeux and Marinescu, 2006) seasonal affective disorder (Sher, 2002), the personality trait of novelty seeking (Grucza *et al*., 2006) and low sense of coherence (Badura *et al*., 2000) is positively related to alcoholism. In addition, low education and low social status have been associated with alcoholism in cross-sectional studies (Fukuda *et al*., 2005; Poznyak *et al*., 2005; Subramanian *et al*., 2005) and longitudinal studies (Wray *et al*., 2005). While large amounts of coffee (Stevenson and Masters, 2005) has been associated with alcohol problems in one cross-sectional study, and longitudinal studies have shown prospective associations between heavy drinking and smoking (Jensen *et al*., 2003) as well as beverage preference (Jensen *et al*., 2002), surprisingly few studies have investigated associations between amount of alcohol consumption and risk of developing alcoholism. Although exposure of alcohol is a necessary link in the complex causal network leading to alcoholism, the empirical relationship between amount of consumption and the risk of developing alcoholism has not been settled. In the present study we prospectively analyzed the relationship between amount of alcohol intake and risk of developing alcoholism in a dataset that enabled us to take sex, educational level, income, smoking, physical exercise, housing status, and marital status, into account.

MATERIALS AND METHODS

Study population

Subjects from the first examination of the Copenhagen City Heart Study (CCHS-I) were used. The CCHS is an ongoing study initially comprising 19 698 men and women over 20 years of age examined in 1976–78. Using the unique Danish personal identification number, the sample was drawn from a population of approximately 90 000 inhabitants living within ten wards surrounding Rigshospitalet, the National University Hospital of Copenhagen. The sample was selected randomly within age and sex strata, and invited by letter to participate. Detailed descriptions of the study have been published elsewhere (Appleyard *et al*., 1989; Hein *et al*., 1993)

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Of the 19 698 invited persons there were 371 persons who died before the examination, and of the remaining 19 327 persons, there were 14 223 (73.6%) responders.

Alcoholism

The 19 698 persons invited to CCHS-I were linked to three different registers in order to determine alcoholism: the Danish Psychiatric Central Research Register, the Danish Hospital Discharge Register, and the Winalco-database. The *Danish Psychiatric Central Research Register* (Munk-Jorgensen and Mortensen, 1997) contains records of all individuals that have been admitted to a psychiatric hospital in Denmark since 1969; the *Danish Hospital Discharge Register* (Jurgensen *et al*., 1986) contains records of all individuals that have been admitted to a Danish hospital since 1976; and the *Winalco-database* (Becker, 2004) contains records of all individuals who have been treated for alcohol problems in the Alcohol Unit, Hvidovre Hospital—an outpatient clinic for alcoholics covering the greater Copenhagen and Frederiksberg municipalities since 1954. Individuals who were given an International Classification of Diseases (ICD) − diagnosis of alcohol abuse in either the Danish Psychiatric Central Research Register or Danish Hospital Discharge Register and individuals who were registered in the Winalco-database were considered to be alcoholic at the given time. The following ICD-8 and ICD-10 diagnoses, including secondary-diagnoses, were in this study used to define alcoholism:

ICD-8: 291.09; 291.19; 291.29; 291.39; 291.99; 303.09; 303.19; 303.20; 303.28; 303.29; 303.90; 303.91; and 303.99.

ICD-10: F10.1; F10.2; F10.3; F10.4; F10.5; F10.6; F10.7; F10.8; F10.9.

In order to test whether a more narrow definition of alcoholism would change our results, we also carried out the analyses using only two diagnoses: ICD-8; 303.20 (chronic alcoholism) and ICD-10; F102 (alcohol dependence).

Alcohol intake

Subjects were asked whether they 'hardly ever/never', 'monthly', 'weekly' or 'daily' drank alcohol, and if this intake was daily the average daily intake was recorded. Thus, an absolute amount of consumed alcohol was obtainable only for persons stating a daily alcohol intake. However, the weekly intake in CCHS-I was calculated on the basis of CCHS-II that contains additional information of the average weekly intake of each beverage type. The weekly amount of consumed alcohol in CCHS-I was obtained by means of a series of regression models estimated from CCHS-II, previously constructed byBecker *et al*. (Becker *et al*., 1995) that includes the explanatory variables age, sex, alcohol intake patterns and the daily alcohol intake. The average weekly intake of beer, wine and spirits was summed to the total alcohol intake (with one bottle of beer being approximately equivalent to the alcohol contents of one glass of wine or one glass of spirits—assuming each drink to contain 12 g of alcohol). The quantitative alcohol intake was divided into the following groups: <1, 1–7, 8–14, 15–21, 22–41, and >41 drinks per week, and the frequency of drinking was measured as hardly ever/never, monthly, weekly or daily.

Covariates

Subjects filled out a self-administered questionnaire containing questions about lifestyle and general health. The following variables were assumed to be possible confounders: Education (less than 8 years, 8–12 years, and more than 12 years); Income (monthly income in 1976–78: <4000, 4000 to 10 000, and >10 000 Danish crowns, which is approximately equivalent to <666, 666 to 1667, and >1667 US$ for exchange rates in 1977); Smoking (never smoker, previous smoker, and current smoker); Physical activity in leisure time (almost completely physically passive or light physical activity <2 h per week, light physical activity 2 to 4 h per week, exhausting physical activity >4 h per week, or regular hard training >4 h per week); Marital status (currently married, or not currently married).

Statistical analyses

The purpose of the analyses was to estimate the hazard ratios (HR) of developing alcoholism by considering the amount and frequency of alcohol consumed, while taking potential confounders into account. Data were analyzed by means of multiple Cox Regression analysis and delayed entry was implemented. To ensure maximal adjustment for confounding by age we used age as the time scale. Subjects were followed from their date of entry, when they received the questionnaire between 1976–78, to the date of their first alcoholic diagnosis, death, disappearance, or emigration or until the end of follow-up (January 2002)—whichever occurred first. Although the Winalco-database was updated until April 2005, the end of follow-up was chosen to be the date where the first register (the Danish Psychiatric Central Register) ended its update. This was done in order to avoid misclassification of alcoholism in the last years of follow-up. Individuals that were registered as alcoholics before 1976–78 were eliminated from the analyses, and in addition to the results shown in the upcoming tables, all analyses were repeated using a time-window of 3 years. Using this time-window we eliminated individuals registered as alcoholics before—and 3 years after they received the questionnaire. The method of 'complete-subject analysis' was used—hence only individuals with values recorded for all covariates in the given analyses were retained. All analyses were stratified according to gender.

In order to investigate the effect of each possible confounder, HRs for developing alcoholism were computed separately for each (Table 2). Secondly, HRs were computed for the quantitative weekly alcohol intake and the frequency of alcohol intake respectively, adjusted for: (i) no covariates, (ii) smoking, (iii) confounders that were significant in a final model built on backwards elimination, and (iv) adjusted for all covariates (Table 3 and 4). All statistical analyses were done by using the statistical software package SAS 9.1.

RESULTS

Of the 19 698 individuals originally invited to participate in CCHS-I, 1566 persons (7.95%) were registered with alcohol problems at least one time in their life. Of the 14 223 individuals who answered the questionnaire, information of

Table 1. Baseline characteristics according to weekly alcohol consumption, Copenhagen City Heart Study, Denmark, 1976–78

	Drinks of alcohol per week:					
	<1	1–7	8–14	15–21	22–41	>41
Proportion of study sample (%)	3090 (21.9)	4856 (34.4)	2740 (19.4)	1495 (10.6)	1294 (9.2)	648 (4.6)
Mean age (years)	56.1	51.4	51.3	52.3	52.4	50.9
Proportion men %	21.9	28.3	57.5	75.4	84.9	92.9
Education <8 years %	64.8	45.0	38.6	40.0	47.5	53.5
Income % lowest	45.6	26.0	21.3	19.0	18.3	23.5
Current smoker %	55.7	61.0	63.7	67.6	74.9	81.9
Physical exercise, % lowest	26.2	16.2	16.8	17.1	10.3	30.5
Living alone %	34.2	26.4	23.4	20.5	24.0	31.5
Never married %	10.7	10.9	10.8	8.5	9.1	9.5
Married current %	58.1	65.6	69.7	74.3	70.5	62.9
Separated/Divorced %	11.5	9.1	8.1	7.8	11.0	18.2
Widow %	12.9	7.2	5.2	4.7	4.4	4.3
Registered alcoholic (%)	117 (3.4)	177(3.2)	143 (4.6)	93(5.7)	166 (11.5)	183 (24.1)
Registered alcoholic before CCHS-I (%)	78 (66.7)	69 (39.0)	44 (30.8)	27 (29.0)	45 (27.1)	66 (36.1)
Registered alcoholic after CCHS-I (%)	39 (33.3)	108 (61.0)	99 (69.2)	66 (71.0)	121 (72.9)	117 (63.9)

Table 2. HRs for the associations between putative confounders at baseline and alcoholism

	Hazard ratio (95% Confidence interval)			
	Men		Women	
Putative confounders:	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Education 12+ years	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Education 8–11 years	1.18 (0.84–1.65)	0.96 (0.69–1.35)	1.02 (0.63–1.66)	1.22 (0.74–2.00)
Education up to 8 years	1.24 (0.89–1.74)	0.96 (0.68–1.34)	0.82 (0.50–1.34)	1.15 (0.69–1.92)
High income	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Middle income	1.12 (0.86–1.46)	1.09 (0.83–1.43)	1.23 (0.83–1.84)	1.42 (0.95–2.13)
Low income	1.70 (1.23–2.35)	1.76 (1.26–2.44)	1.06 (0.67–1.67)	1.40 (0.88–2.22)
Never smoker	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Previous smoker	1.40 (0.84–2.34)	1.22 (0.73–2.15)	1.72 (0.91–3.25)	1.35 (0.70–2.58)
Current smoker	2.45 (1.57–3.81)	1.87 (1.19–2.92)	4.08 (2.56–6.50)	3.30 (1.06–5.28)
Exercise, hard	1.00 (reference)	1.00 (reference)	1.00 (Reference)	1.00 (Reference)
Exercise, more than 4 h	0.88 (0.47–1.66)	1.00 (0.52–1.93)	0.53 (0.17–1.72)	0.69 (0.21–2.24)
Exercise, 2–4 h	0.96 (0.52–1.77)	1.06 (0.56–2.01)	0.45 (0.14–1.43)	0.61 (0.19–1.94)
Exercise, less than 2 h	1.68 (0.90–3.15)	1.62 (0.84–3.12)	0.73 (0.23–2.35)	0.84 (0.26–2.71)
Living with someone	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Living alone	2.25 (1.81–2.81)	1.94 (1.55–2.43)	1.03 (0.76–1.41)	0.96 (0.70–1.31)
Married at some time	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Never married	1.70 (1.24–2.33)	1.91 (1.39–2.62)	0.95 (0.59–1.56)	1.03 (0.63–1.68)
Married now	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Not married now	2.34 (1.89–2.89)	2.03 (1.64–2.52)	1.15 (0.87–1.53)	1.09 (0.82–1.46)
Being up to 40 years old	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Being over 40 years old	0.66 (0.52–0.83)	0.53 (0.39–0.71)	0.22 (0.16–0.31)	0.19 (0.12–0.29)

[a] Adjusted for drinks of alcohol per week and smoking.

the amount of alcohol consumed each week was available for 14 123 participants—of these, 879 persons (6.22%) were registered as alcoholics while 11 074 persons died or emigrated during the follow-up period.

The proportion of men and the proportion of smokers increased with higher alcohol consumption. The proportion of participants who consumed more than 41 drinks per week was relatively young, did little exercise, was frequently separated or divorced, and was more frequently registered as alcoholics than participants in the other consumption categories (Table 1).

Investigating the HRs for each confounder showed that for women, being a current smoker and being under 40 years of age increased the risk of developing alcoholism. Low income, being a current smoker, living alone, being unmarried, and being under 40 years were risk factors for men (Table 2).

The risk of alcoholism varied according to the quantitative weekly alcohol-intake (Table 3), and the limit where the risk increased significantly was rather different for men and women respectively. For women, there was a strong dose-dependent increase in risk of alcoholism with increased alcohol intake, hence the crude HR was 1.91 when drinking

Table 3. HRs for the associations between weekly alcohol intake at baseline and alcoholism

	Women				Men			
Number drinks:	Unadjusted	Adjusted for smoking	Adjusted[a]	Complete adjustment[b]	Unadjusted	Adjusted for smoking	Adjusted*	Complete adjustment†
<1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1–7	1.91	1.83	1.83	2.02	1.01	0.98	1.06	1.16
	(1.21–3.02)	(1.16–2.88)	(1.16–2.88)	(1.16–3.53)	(0.54–1.89)	(0.53–1.83)	(0.57–1.97)	(0.61–2.20)
8–14	3.26	3.11	3.11	3.26	1.49	1.44	1.56	1.71
	(1.98–5.37)	(1.88–5.12)	(1.88–5.12)	(1.78–5.98)	(0.83–2.66)	(0.80–2.57)	(0.87–2.80)	(0.93–3.13)
15–21	6.14	5.38	5.38	5.62	1.43	1.39	1.52	1.71
	(3.52–10.70)	(3.08–9.40)	(3.08–9.40)	(3.00–10.49)	(0.78–2.63)	(0.76–2.55)	(0.83–2.79)	(0.91–3.20)
22–41	7.99	6.97	6.97	7.69	3.99	3.74	3.81	4.21
	(4.31–14.82)	(3.75–12.94)	(3.75–12.94)	(3.88–15.24)	(2.28–6.97)	(2.14–6.54)	(2.18–6.68)	(2.35–7.53)
>41	39.84	30.20	30.20	30.66	8.22	7.48	7.13	7.84
	(20.92–75.89)	(15.81–57.70)	(15.81–57.70)	(15.18–61.93)	(4.69–14.39)	(4.27–13.12)	(4.06–12.51)	(4.37–14.04)

[a] Adjusted only for confounders that were significant in the model (Women: smoking; men: smoking, exercise, and married/unmarried.).
[b] Adjusted for: education, income, smoking, physical exercise in leisure time, living alone/living with someone, and married/unmarried.

Table 4. HRs for the associations between frequency of alcohol intake at baseline and alcoholism; not adjusted for weekly alcohol intake

	Women				Men			
Number drinks:	Unadjusted	Adjusted for smoking	Adjusted[a]	Complete adjustment[b]	Unadjusted	Adjusted for smoking	Adjusted*	Complete adjustment†
Never/ almost never	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Monthly	1.75	1.69	1.69	2.06	0.86	0.83	0.91	1.00
	(1.08–2.85)	(1.04–2.76)	(1.04–2.76)	(1.20–3.54)	(0.46–1.60)	(0.45–1.55)	(0.49–1.70)	(0.53–1.90)
Weekly	2.66	2.48	2.48	2.94	1.42	1.38	1.51	1.68
	(1.62–4.35)	(1.51–4.06)	(1.51–4.06)	(1.70–5.10)	(0.82–2.49)	(0.79–2.41)	(0.86–2.64)	(0.94–2.99)
Daily	6.93	6.21	6.21	7.15	3.55	3.30	3.42	3.79
	(4.32–11.11)	(3.86–9.98)	(3.86–9.98)	(4.20–12.17)	(2.11–5.99)	(1.96–5.57)	(2.03–5.77)	(2.20–6.52)

[a] Adjusted only for confounders that were significant in the model (Women: smoking; men: smoking, physical exercise in leisure time, and married/unmarried.)
[b] Adjusted for: education, income, smoking, physical exercise in leisure time, living alone/living with someone, and married/unmarried.

1–7 drinks per week (95% confidence interval (CI): 1.21, 3.02), 3.26 when drinking 8–14 drinks per week (95% CI: 1.98–5.37), and 39.84 (95% CI: 20.92–75.89) when drinking more than 41 drinks per week. For men, however, the risk of developing alcoholism only increased with consumption of more than 21 drinks per week. The HR for drinking 22–41 drinks per week was 3.99 (95% CI: 2.28–6.97) and the HR for >41 drinks per week was 8.22 (95% CI: 4.69–14.39). After adjustment for smoking, the HRs diminished slightly, but the significances of the unadjusted results were not altered. Using backwards elimination, only smoking was a significant confounder for women, while smoking, physical exercise, and marital status were significant confounders for men. Neither adjusting for factors that were significant in the final model, nor adjusting for all possible confounders chosen in the present study changed the HRs considerably (Table 3).

Frequency of alcohol intake was also positively associated with the risk of alcoholism (Table 4). For women, the risk increased dose-dependently with higher frequency, hence the raw HR for drinking monthly was 1.75 (95% CI: 1.08–2.85) compared to never/almost never drinking, 2.66 (95% CI: 1.62–4.35) for drinking weekly, and 6.93 (95% CI: 4.32–11.11) for drinking daily. Men only increased their risk of developing alcoholism if they had a daily alcohol intake (HR = 3.55, 95% CI: 2.11–5.99). The HRs were not adjusted for the amount of weekly alcohol intake; however the risk did not alter considerably by controlling for other confounders, and using backwards elimination, it was the same confounders that were significant as it was in Table 3.

Inserting a time-window of 3 years did not change the results in neither Table 3 nor 4 notably. In both tables, the HR's for women decreased slightly while the HR's for men increased a little; however, the significances of the results were the same. Using a more narrow definition of alcoholism with only two diagnoses meant that there were fewer cases of alcoholism −31 for women and 96 for men. Hence, it was not possible to carry out Cox regression analyses for women. For men however, the significances of the results did not alter, although the HR's were smaller (data not shown).

DISCUSSION

We have demonstrated that alcohol—not very surprisingly—is a strong predictor of developing alcoholism. In addition, however, our findings suggest different thresholds of harmful drinking in relation to alcoholism among men and women, since women increase their risk by much smaller

amounts and frequencies than men. Smoking had an independent effect on the risk of alcoholism for both men and women. Physical exercise and marital status confounded the risk for men, while education, income, and housing status were not significant confounders.

The present study was based on a large study population sample, and because of the prospective design, selection and recall bias was minimized. The follow-up time of 26 years meant that we were able to discover the majority of outcomes of alcoholism that expectably will ever occur for the study population—although several persons were eliminated from the analyses due to diagnosis before 1976–78. Long duration of follow-up is usually considered to be a strength in prospective cohort studies, as the number of cases, and hence the statistical power, will increase. However, in the present study, the long follow-up time probably implied individual changes in exposure, as changes in alcohol intake have occurred during the follow-up period. Since the self-reported questionnaire was not validated by biochemical markers or interviews, the assessment of alcohol consumption may be biased. Self-reports of alcohol consumption and alcohol problems are generally believed to be biased towards an underestimation among the heaviest drinkers (Poikolainen, 1985), which would diminish the statistical power of the analyses for the groups with highest alcohol intake—this misclassification is possibly sex-specific (Gronbaek and Heitmann, 1996). Misclassification of outcome is also plausible, as the concept of alcoholism in this study was defined as having being admitted to a hospital with an alcohol related diagnosis or having attended an outpatient clinic for alcoholics. With these register data only the most severe cases of alcoholism can be expected to be detected, but nevertheless, we found a rather high percentage of alcoholism, 6.22%, among the respondents.

Alcoholics diagnosed before answering the questionnaire in 1976–78 were eliminated from the analyses. It is, however, likely that people were alcoholics for a period of time before they were registered, and consequently the presented analysis would include a sub-sample of individuals that are already alcoholic, but are not yet registered. To evaluate the size of this problem we inserted a time-window of 3 years, but analyses based on this reduced sample essentially showed the same results as presented in the tables, and consequently we assume that undiagnosed alcoholics did not seriously bias our results.

It is generally assumed that non-response is associated with increased alcohol consumption (Lahaut *et al*., 2002), and according to our results, non-responding was also associated with alcoholism—8% of the invited persons were defined as alcoholics while only 6% of the respondents were defined as alcoholics. Consequently, selection bias may have occurred, which may limit the generalizability of our results. However, there are no strong reasons to believe that the relation between alcohol intake and alcoholism is different among responders and non-responders and that non-responding has seriously affected the obtained HRs.

While other studies have mainly used the diagnosis, 'alcohol dependence' (Caetano *et al*., 1997; Caetano and Cunradi, 2002), the definition of alcoholism was based on information from three alternative registers. Using a more strict definition of alcoholism based on only two diagnoses, too few cases were observed among women to carry out Cox regression analyses. For men, however, we found that analyses based on the strict definition showed the same patterns of significant associations—only the HR's were smaller.

Age has previously proven to be an important predictor of developing alcoholism (Hingson *et al*., 2006a,b), and in our study, age also seemed to affect the risk, as respondents over 40 years of age had a decreased risk of developing alcoholism (Table 2). However, in order to retain a sufficient number of cases in each sub-category, the analyses were not stratified according to age. Nevertheless, age was the underlying timescale in our regression analyses, and therefore the modifying role of age was controlled for in all HRs.

An important aspect of the present study is the fact that the average year of birth among the respondents was 1924—suggesting possibly important differences between this study population and younger generations. Especially among women, differences in drinking patterns and alcohol-culture may make it difficult to generalize our results to younger women. The fact that even very small amounts of weekly alcohol intake implied increased risk of developing alcoholism for women in our study sample, may reflect the fact that alcohol consumption was relatively rare in women, and that the categories of drinking women included sub samples of vulnerable women, exposed to several other risk-factors and perhaps being genetically at risk.

To our knowledge, the association between the amount and frequency of alcohol intake and risk of developing alcoholism has not been documented in other studies. However, studies have shown that overall alcohol intake is a good predictor of alcohol-related harm. A Finnish study showed, that the probability of alcohol-related consequences increases with the annual intake of alcohol (Makela and Simpura, 1985), and several studies have found associations between heavy drinking patterns and increased risks for alcohol-related consequences such as drunk driving, injuries, job problems and criminality (Cherpitel *et al*., 1995; Midanik *et al*., 1996; Greenfield, 1998; Greenfield and Rogers, 1999).

Several of the covariates included in the present study such as economic status, educational level, smoking, and beverage preference have been shown to be associated with alcoholism in other studies (Jensen *et al*., 2002; Sher, 2002; Jensen *et al*., 2003; Subramanian *et al*., 2004; Averina *et al*., 2005). In this study we used CCHS-I that contained information on various lifestyle related risk factors; but many other factors may modify the association between amount of alcohol consumption and risk of developing alcoholism. These factors include individual characteristics as well as a number of social factors described in the introduction, and we believe that future research would gain much by exploring how these factors affect the relation between alcohol and alcoholism.

In conclusion, we found that both the amount *and* frequency of alcohol intake was positively associated with later risk of developing alcoholism, and that the risk for women increased with very low levels of consumption while the risk for men only increased with consumption of more than 21 units per week.

Danish, and several other national drinking limit recommendations for alcohol intake, are 14 and 21 drinks for women and men respectively. Seen in the light of alcoholism, the present study confirms the fact that that these limits may be relevant for men. Women, however, appear to be very

susceptible to alcohol consumption, as their risk for alcoholism increases significantly by much lower intakes than 14 drinks per week. We find it important that research is conducted to clarify whether this striking sex-difference can be demonstrated in younger generations.

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Paper II

Beverage Preference and Risk of Alcohol-Use Disorders: A Danish Prospective Cohort Study*

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ABSTRACT. Objective: The purpose of this study was to examine whether preferred type of alcoholic beverage influences the later risk of alcohol-use disorders (AUD). **Method:** A prospective cohort study was used, comprising three updated measures of alcohol intake and covariates, and 26 years of follow-up data on 18,146 individuals from the Copenhagen City Heart Study, Denmark. The study population was linked to three different registers to detect AUD registrations. **Results:** For both genders, wine drinking was associated with lower risk of AUD irrespective of the weekly amount of alcohol consumed. Women drinking 15-21 drinks per week of only beer and distilled spirits had a risk of 15.8 (95% confidence interval [CI]: 7.8-33.3) for AUD, whereas those whose total alcohol intake comprised more than 35% wine had a risk of 2.0 (CI: 0.7-5.2). Men drinking 15-21 drinks per week of only beer and distilled spirits had a risk of 3.1 (CI: 1.8-5.4), whereas those whose total alcohol intake comprised more than 35% wine had a risk of 0.8 (CI: 0.3-2.1). Consuming more than 35% beer increased the risk of AUD for women, whereas the percentage of distilled spirits intake did not influence the risk of AUD for either women or men. **Conclusions:** Individuals who include wine when they drink alcohol have lower risks of AUD, independent of the total amount of alcohol consumed. The most likely explanation of these results is that lifestyle factors and personal characteristics are associated with beverage preference. (*J. Stud. Alcohol Drugs* **69:** 371-377, 2008)

PREVIOUS STUDIES OF THE RELATIONSHIP between alcohol intake and subjective health (Gronbaek et al., 1999), risk of stroke (Truelsen et al., 1998), hip fracture (Hoidrup et al., 1999), lung cancer (Prescott et al., 1999), prostate cancer (Baglietto et al., 2006b), gastric cancer (Barstad et al., 2005), alcohol-induced cirrhosis (Becker et al., 2002), dementia (Truelsen et al., 2002), and mortality (Baglietto et al., 2006a; Gronbaek et al., 1995, 2000a; Kauhanen et al., 1997; Strandberg et al., 2007) suggest that different types of beverage have different health-related outcomes. Although alcohol is obviously a necessary element in the complex causal network leading to the development of alcohol-use disorders (AUD), it has not yet been investigated whether preferred type of alcoholic beverage influences this risk. An earlier study found that moderate wine drinkers appear to be at lower risk of becoming heavy and excessive drinkers compared with moderate beer drinkers (Jensen et al., 2002), but in this study information on AUD was not included. Other studies have reported associations between beer drinking and development of alcohol-related problems (Smart and Walsh, 1999) and between beer drinking and unsafe behaviors such as driving while intoxicated (Berger and Snortum, 1985; Gruenewald et al., 2000; Greenfield and Rogers, 1999).

The aim of the present study was to analyze whether preferred type of alcoholic beverage influences the later risk of developing AUD in a large Danish prospective cohort study. Our hypothesis was that wine drinkers were at lower risk of developing AUD. Subjects were categorized according to both the percentage of each beverage type of their total alcohol consumption and according to their total alcohol intake. The analyses were conducted for women and men separately and were adjusted for smoking, cohabitation status, income, and education.

Method

Study population

Data from the Copenhagen City Heart Study (CCHS) were used (Appleyard et al., 1989; Hein et al., 1993). The

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CCHS is an ongoing study initially comprising 19,698 men and women age 20 and older examined in 1976-1978 who were randomly drawn in January 1976 from the Copenhagen Population Register, by using the unique Danish personal identification number consisting of date of birth and a registration number. The sample was drawn from a population of approximately 90,000 inhabitants living in the Copenhagen area. The selected individuals were chosen randomly within age and gender strata and invited by letter to answer self-administered questionnaires in 1976-1978, 1981-1983, and 1991-1993. In 1976-1978 (CCHS-I), 14,223 respondents returned the questionnaire, corresponding to 74% of the invited individuals. In the 1981-1983 follow-up (CCHS-II) all previously invited plus 500 new participants were enrolled (response rate = 70%), and in the 1991-1993 follow-up (CCHS-III), nearly 3,000 new participants were enrolled (response rate = 61%). Detailed descriptions of the study have been published elsewhere (Appleyard et al., 1989; Hein et al., 1993).

Alcohol-use disorders

The total sample of 23,189 invited individuals was linked to three different registers to determine AUD: the Danish Hospital Discharge Register (Jurgensen et al., 1986) contains records of all individuals who have been admitted to a Danish hospital since 1976; the Danish Psychiatric Central Research Register (Munk-Jorgensen and Mortensen, 1997) contains records of all individuals who have been admitted to a psychiatric hospital in Denmark since 1969; and the WINALCO database (Becker, 2004) contains records of all individuals treated for alcohol problems in the Alcohol Unit, Hvidovre Hospital—an outpatient clinic for alcoholics covering the greater Copenhagen and Frederiksberg municipalities since 1954. Individuals who had been given an International Classification of Diseases (ICD)-8 or ICD-10 diagnosis of AUD in either the Danish Psychiatric Central Research Register or Danish Hospital Discharge Register and individuals who were registered in the WINALCO database were considered to have an AUD at the given time. In this study, AUDs comprised the following ICD-8 and ICD-10 diagnoses: ICD-8 (303 [alcoholism]) and ICD-10 (F10.1 [harmful use] and F10.2 [dependence syndrome]).

Alcohol intake

In CCHS-I, participants were asked according to each beverage type (beer, wine, and distilled spirits) whether they drank "hardly ever/never," "monthly," "weekly," or "daily," and, for daily consumers, the average daily intake was recorded. In CCHS-II and CCHS-III, information of the average weekly intake of each beverage type was obtained for all participants. The weekly amount of consumed alcohol in CCHS-I was obtained by means of a series of regression models estimated from CCHS-II by Becker et al. (1995) that includes the explanatory variables of age, gender, alcohol intake patterns, and the daily alcohol intake.

The average weekly intake of beer, wine, and distilled spirits was summed to the total alcohol intake—one drink of any type was assumed to contain 12 g of alcohol. The intake was classified into the following groups: 0, 1-6, 7-14, 15-21, and >21 drinks per week. In addition, the percentage of each type of the total alcohol intake was calculated and classified into the following categories: <1%, 1%-35%, and >35%. For interpretation of the results, other classifications of the percentage of each beverage type were tested. Hence the analyses were supplemented using the following categories: <1%, 1%-15%, 16%-35%, and >35%, and <1%, 1%-15%, 16%-50%, and >50% (data not shown).

Covariates

Preference for different types of alcoholic beverages may be associated with demographic and lifestyle characteristics that affect the risk of developing AUD. The following variables were assumed to be possible confounders *and* were available in all three data-collection follow-ups: education (less than 8 years, 8-12 years, and more than 12 years); income (three monthly income groups: lowest, middle, and highest); smoking (never smoker, previous smoker, and current smoker); and cohabitation status (living with someone, living alone).

Statistical analyses

The purpose of the analyses was to estimate the hazard ratios of developing AUD by considering the type of alcohol consumed. Data were analyzed by means of multiple Cox regression analysis with repeated measurements, and delayed entry was implemented. To ensure maximal adjustment for confounding by age, we used age as the time scale. Subjects were followed from their date of entry, when they received the questionnaire between 1976 and 1993, to the date of their first diagnosis related to AUD, death, disappearance, or emigration, or until the end of follow-up (January 2002)—whichever occurred first. To avoid misclassification of AUD in the last years of follow-up, the end of follow-up was chosen to be the date where the first register (the Danish Psychiatric Central Register) ended its update. Individual alcohol intake is most likely to change over time, and because both alcohol intake and information on covariates were measured at regular intervals in 1976-1978, 1981-1983, and 1991-1993, updated measures of alcohol intake and covariates were used. In these analyses, we

TABLE 1. Baseline characteristics of the study population, in the first round of the Copenhagen City Heart Study (CCHS), 1976-1978

Variable	*n* (%)	Alcoholic drinks per week, mean	Age years, mean	Men, %	Smokers, %	Living alone, %	Lowest income group, %	Education <8 years, %	Registered with AUD, %	Registered with AUD after CCHS-I, %
Weekly alcohol intake										
<1 drink	3,112 (21.9)	–	56.1	22.0	55.9	34.2	45.9	65.1	3.9	1.8
1-6 drinks	4,313 (30.4)	–	52.2	26.5	60.8	27.1	27.2	46.8	3.5	2.2
7-14 drinks	3,313 (23.3)	–	50.3	55.1	63.7	23.1	20.9	37.7	4.9	3.3
15-21 drinks	1,500 (10.6)	–	52.3	75.3	67.7	20.5	19.1	39.9	6.1	4.5
>21 drinks	1,955 (13.8)	–	51.9	87.6	77.3	26.6	20.2	49.6	17.9	13.0
Beer[a]										
<1%	3,870 (27.3)	2.2	55.9	19.0	56.1	34.4	41.7	59.3	4.1	1.8
1%-35%	3,604 (25.4)	7.8	52.2	26.4	60.1	26.3	23.4	40.0	3.2	2.3
>35%	6,714 (47.3)	16.4	50.9	71.6	69.4	23.0	22.5	46.5	9.0	6.1
Wine[a]										
<1%	5,004 (35.4)	9.0	56.2	56.6	63.4	32.4	41.7	64.8	7.8	4.3
1%-35%	4,542 (32.1)	14.8	50.9	74.1	69.9	20.3	19.1	43.5	7.3	4.9
>35%	4,609 (32.6)	7.3	50.3	20.2	56.7	27.6	21.5	35.2	3.2	2.5
Distilled spirits[a]										
<1%	4,716 (33.3)	6.4	54.9	31.3	59.4	32.7	39.9	59.3	6.2	3.2
1%-35%	7,171 (50.7)	12.4	49.8	56.6	65.1	23.1	19.5	41.1	6.1	4.2
>35%	2,272 (16.1)	11.9	56.6	41.6	66.1	27.0	29.8	48.2	6.1	4.3

Notes: AUD = alcohol-use disorder. [a]Percentage of total alcohol intake.

prospectively assessed the risk of AUD in between examination increments based on determinations of beverage preference and other covariates derived from the preceding questionnaire.

In case of missing data about alcohol intake, smoking, income, or education, the last observation was carried forward to maintain a large study population (cohabitation status was not carried forward, because we did not consider it realistic to assume this factor to be a constant). Individuals who were registered with AUD before their date of entry were eliminated from the analyses, and, to avoid bias because of existing AUD at the time of measuring exposure, all analyses were repeated using a time window of 2 years for entrance to the study and for each subject's update of variables. Using this time window, we aimed to eliminate reverse causation of the influence of AUD on patterns of alcohol intake.

Characteristics of the study population are shown for subjects who entered the study at the first examination in 1976-1978 (Table 1). All Cox regression models included percentage of each beverage type respectively (three levels), weekly amount of alcohol (five levels), smoking habits (three levels), cohabitation status (two levels), income (three levels), and education (three levels). Analyses were stratified according to gender and were done by using the statistical software package SAS Version 9.1 (SAS Institute Inc., Cary, NC).

Results

Of the 23,198 invited individuals, 1,756 persons (7.6%) were registered at least once with AUD. Of the 18,146 individuals who completed as a minimum one of the three questionnaires, 1,200 persons (6.6%) were registered with AUD.

Descriptive results

In CCHS-I, men were more likely to prefer beer than women. Thus, 71.6% of the subjects consuming more than 35% beer were men, and only 20.2% of the subjects consuming more than 35% wine were men. A higher percentage of those preferring to drink beer and distilled spirits than those preferring to drink wine developed AUD. Thus, 6.1% and 4.3% of those drinking more than 35% beer or distilled spirits, respectively, later developed AUD, whereas only 2.5% of those consuming more than 35% wine developed AUD (Table 1). The average age of first-time registration with AUD was generally lower for those preferring to drink beer compared with those preferring to drink distilled spirits or wine. However, age at AUD did not have any relation to the weekly percentage of wine intake (data not shown).

In CCHS-I, compared with beer and distilled spirits drinkers, subjects consuming more than 35% wine were generally characterized as having a lower weekly alcohol intake and being younger, female, less likely to smoke, more likely to live alone, and less likely to be in the lowest income group or to have an education of less than 8 years (Table 1).

Table 2 shows how beverage preferences changed during the 15 years of investigation. Beer was the most common beverage type in 1976-1978, with 47.3% of the study population's intake consisting of more than 35% beer. In

TABLE 2. Overview of drinking patterns in the three Copenhagen City Heart Studies (CCHSs)

Variable	CCHS-I (1976-1978) *n* (%)	CCHS-2 (1981-1983) *n* (%)	CCHS-3 (1991-1993) *n* (%)
Nondrinkers	3,112 (21.9)	3,929 (31.0)	2,300 (23.0)
>21 drinks per week	1,955 (13.8)	1,292 (10.2)	1,162 (11.6)
Beer			
<1%	3,870 (27.3)	5,948 (47.0)	4,039 (40.4)
1%-35%	3,604 (25.4)	1,850 (14.7)	2,055 (20.6)
>35%	6,714 (47.3)	4,862 (38.4)	3,906 (39.1)
Wine			
<1%	5,004 (35.4)	6,840 (54.0)	3,897 (39.0)
1%-35%	4,542(32.1)	2,247 (17.7)	2,039 (20.4)
>35%	4,609 (32.6)	3,578 (28.3)	4,063 (40.6)
Distilled spirits			
<1%	4,716 (33.3)	8,055 (63.6)	6,280 (62.9)
1%-35%	7,171 (50.7)	2,802 (22.1)	2,499 (25.0)
>35%	2,272 (16.1)	1,802 (14.2)	1,213 (12.1)

1991-1993, 40.6% of the study population had an alcohol intake consisting of more than 35% wine, compared with 32.6% in 1976-1978 (Table 2).

Wine and alcohol-use disorders

For both genders, subjects who drank no wine had an increased risk of developing AUD, even for low amounts of weekly alcohol intake (Figures 1 and 2). Among women, the increased risk was especially obvious for those drinking 15-21 drinks per week. Of these women, those who drank only beer and distilled spirits had a risk of 15.8 (CI: 7.8-33.3) for developing AUD, and those whose total alcohol intake comprised more than 35% wine had a risk of 2.0 (CI: 0.7-5.2) when the hazard ratios were set to 1.0 among nondrinkers (Figure 1). Men drinking 15-21 drinks per week of only beer and distilled spirits had a risk of 3.1 (CI: 1.8-5.4), whereas those whose total alcohol intake comprised more than 35% wine had a risk of 0.8 (CI: 0.3-2.1) (Figure 2). Supplementing the analyses with different categorizations of percentage of wine showed that wine intake did not have a dose-responsive effect on the risk of AUD. Hence, only respondents drinking no wine differed significantly from the other groups according to risk of AUD (data not shown), and therefore the effect of wine seems to be an "all-or-none" effect. Inserting a time window of 2 years, the patterns of Figures 1 and 2 generally remained the same. However, the risks for women generally became lower for all categories of alcohol intake and percentage of wine, whereas the risks for men generally became higher. In addition, the differences in risk between nonwine drinkers and wine drinkers decreased for women, whereas the differences increased for men (data not shown).

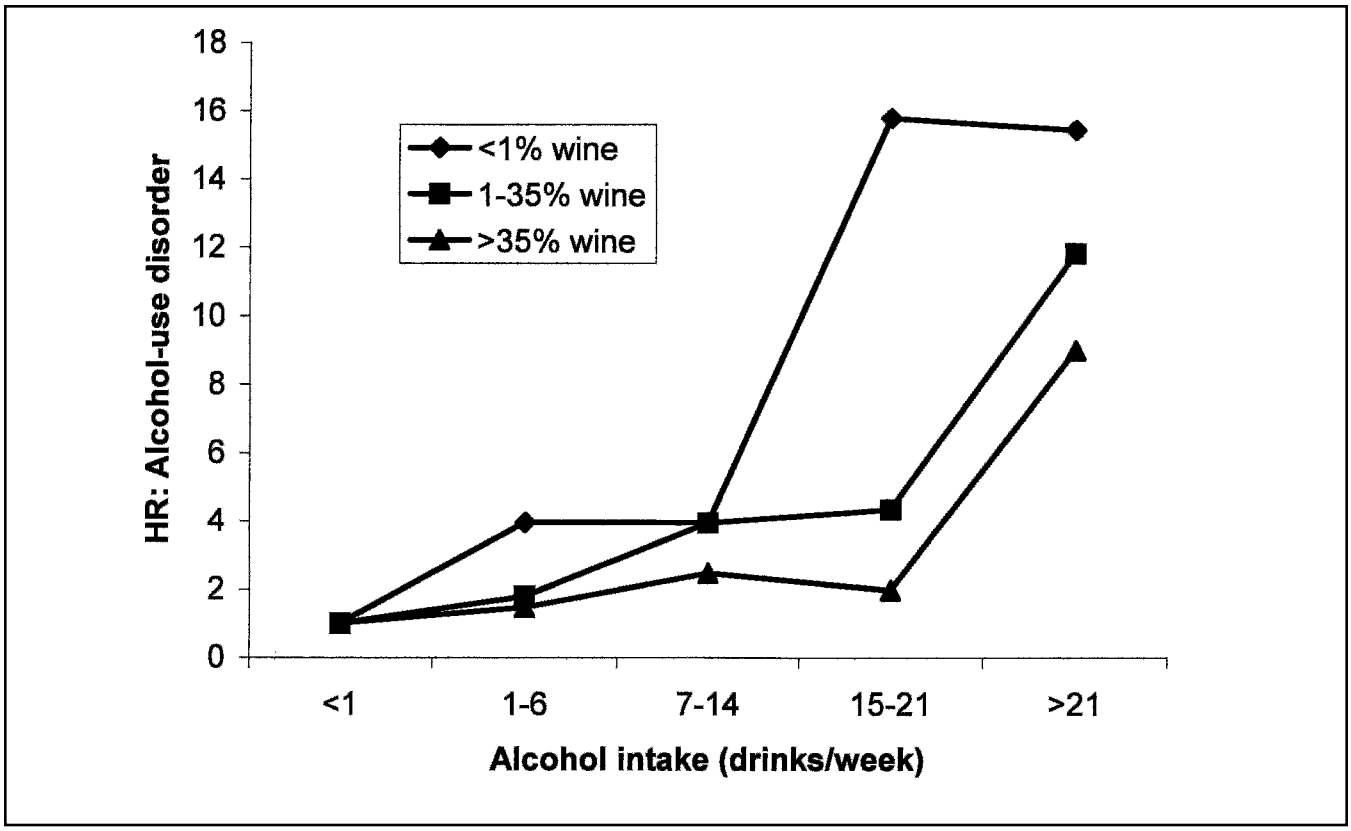

FIGURE 1. Risk of alcohol-use disorder for women according to percentage of wine in total alcohol intake and according to total alcohol intake. Hazard ratios (HRs) are set to 1.0 among nondrinkers and are adjusted for smoking, cohabiting status, income, and education.

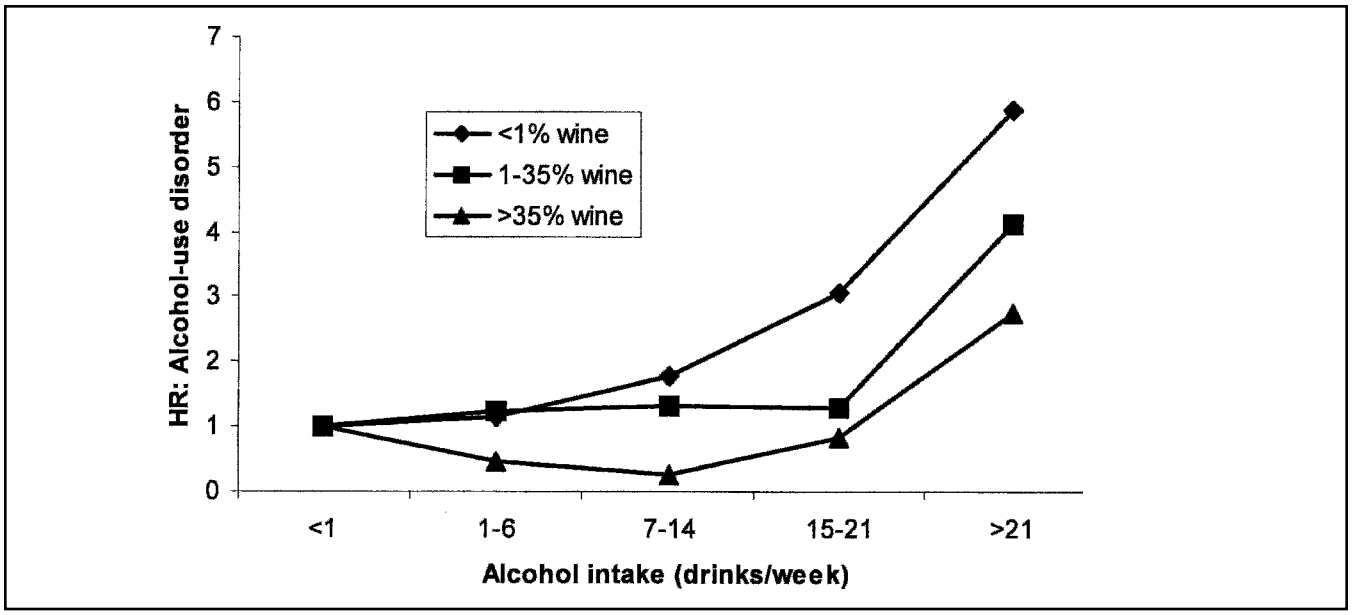

FIGURE 2. Risk of alcohol-use disorder for men according to percentage of wine in total alcohol intake and according to total alcohol intake. Hazard ratios (HRs) are set to 1.0 among nondrinkers and are adjusted for smoking, cohabiting status, income, and education.

Beer, distilled spirits, and alcohol-use disorders

The results for beer and distilled spirits are not illustrated, but consumption of more than 35% beer increased the risk of AUD for women for all classifications of weekly alcohol intake. Hence, women who drank 15-21 drinks per week with beer comprising more than 35% had a risk of 10.9 (5.8-20.5), whereas the risk was 3.3 (1.1-9.6) if the intake contained no beer. The percentage of beer did not have any clear influence on the risk for AUD in men, just as the percentage of distilled spirits intake did not influence the risk of AUD for either women or men.

Discussion

The present study suggests that wine drinking is associated with lower risk of developing AUD independent of the total amount of alcohol consumed. Both women and men who drank only beer and distilled spirits were more likely to develop AUD than those with wine comprising 35% or more of their total alcohol intake. Additionally, women drinking more than 35% of their total alcohol intake as beer showed increased risk of AUD, whereas this was not the case for male beer drinkers. The percentage of distilled spirits in the total consumption was not associated with the risk of AUD in men or women.

The beneficial effect of wine

The beneficial effects of wine compared with beer and distilled spirits have been found in several previous studies in relation to other health outcomes (Baglietto et al., 2006a,b; Barstad et al., 2005; Becker et al., 2002; Gronbaek et al., 1995, 1999, 2000a; Hoidrup et al., 1999; Kauhanen et al., 1997; Prescott et al., 1999; Strandberg et al., 2007; Truelsen et al., 1998; Truelsen et al., 2002). We believe that there are two explanations for our findings. One explanation is that both beverage preference and AUD are strongly associated with lifestyle and personality factors that we were unable to adjust for in this study. Another explanation is that substances other than ethanol in beer, wine, and distilled spirits may have different effects on the development of alcohol dependence and therefore the risk of developing AUD.

Several studies support the first explanation. A prospective study showed that, irrespective of socioeconomic status, high intelligence was associated with preference for wine over other alcoholic beverages (Mortensen et al., 2005), and a cross-sectional study found that wine drinking was associated with optimal social, intellectual, and personality functioning, whereas beer drinking was associated with suboptimal characteristics (Mortensen et al., 2001). Other cross-sectional studies found that wine drinking was associated with a healthier diet (Tjonneland et al., 1999; Johansen et al., 2007), better education (Klatsky et al., 1990), fewer disease symptoms (Klatsky et al., 1990), and higher quality of life (Strandberg et al., 2007). Wine-only drinkers have been shown to be intoxicated less often than drinkers with other preferences (Smart and Walsh, 1999), which decreases the risk for the many consequences associated with acute intoxication, such as accidents, injuries, acute interpersonal problems, and alcohol dependence (Babor et al.,

2003). Beer drinkers have been shown to be more likely to underestimate the intoxicating effects of drinking compared with drinkers who prefer other alcoholic beverage types, and among adolescents it was shown that drinkers of beer and distilled spirits were more rebellious and deviant, whereas wine drinking appeared to be the beverage of moderation (Smart and Walsh, 1995). If wine drinkers are mainly steady drinkers and beer and distilled spirit drinkers are mainly binge drinkers, drinking pattern may explain the apparent differences in the effects of beer, wine, and distilled spirits on AUD. However, studies showed that for a given average intake, beer drinkers are more likely to have a frequent intake than wine drinkers and are thus less likely to be binge drinkers (Gronbaek et al., 2000b; Gruenewald et al., 2000). Beverage preference may be related to quantity and quality of social network and social relations, and this may partly explain the association between beverage preference and AUD. Finally, wine is often consumed during meals, allowing for more social control over drinking in addition to the fact that blood alcohol concentrations may be lower when drinking is accompanied by food intake.

We have been unable to locate studies suggesting that substances other than ethanol in beer, wine, and distilled spirits may have different effects on the development of alcohol dependence. Biological explanations of possible protective factors in wine with respect to risk of developing AUD have not yet been proposed. In addition, when we supplemented our results in Figures 1 and 2 with analyses of different categorizations of percentage of wine (<1%, 1%-15%, 16%-35%, >35%, and <1%, 1%-15%, 16%-50%, >50%), the protective effect of wine was not dose-responsively related to the percentage of wine in total alcohol consumption, and the difference between drinkers who prefer wine and drinkers who prefer beer and distilled spirits seems to be an all-or-none phenomenon. This makes it very unlikely that the low risk of AUD associated with wine is an effect of protective substances, because an effect of ingredients would be expected to be dose dependent and, among wine drinkers, to show a relationship with the percentage of wine consumed. Consequently, we find it likely that the observed protective effect of wine reflects differences in lifestyle factors and personal characteristics between wine drinkers and nonwine drinkers that could not be controlled for in the present study.

Methodological issues

Because of the prospective design of the present study, selection and recall bias were minimized. The follow-up time of 26 years means that registration of cases with AUD should be as complete as possible in a register-based study. In Denmark, all residents have equal access to psychiatric hospitals and all treatments are free of charge. However, misclassification of our outcome was still plausible, because the concept of AUD in this study was defined as having being admitted to a hospital with an AUD diagnosis or having attended an outpatient clinic for individuals with AUD. With register-based data, only the most severe cases of AUD are likely to be detected. In this study, 6.6% of the respondents were categorized as having AUD; however, no valid prevalence data exist on AUD in Denmark.

Self-reports of alcohol consumption and alcohol problems are generally believed to be biased toward underestimation among the heaviest drinkers (Poikolainen, 1985), and this bias may be gender specific (Gronbaek and Heitmann, 1996). If beverage preference is associated with whether a person's alcohol problems bring him or her to medical attention, it could have biased our findings. However, it was not possible to analyze this association in the present study. Information in each of the three questionnaires on self-reported intake of beer, wine, and distilled spirits was assumed to be an indicator of each respondent's average intake of these beverages over a longer period. Changes in alcohol intake may be beverage-specific, and this could bias our results. Thus, if beer and distilled spirits drinkers tend to increase their level of alcohol consumption more than wine drinkers, this may explain the apparent beneficial effect of wine in our study. However, no studies have demonstrated this to be the case, and by analyzing repeated measurements we endeavored to use the available information optimally (although treating carried-forward data as observed data might have resulted in bias).

Conclusion

We conclude that individuals who include wine when they drink alcohol have lower risks of developing AUD, independent of the total amount of alcohol consumed. Our findings may have two explanations. Either we were not able to take fully into account the differences in lifestyle and personal characteristics associated with beverage preference when we adjusted our analyses for possible confounders, or, alternatively, ingredients in beer and distilled spirits may be associated with the risk of developing AUD. We do not know of any such substances, and, as our analyses did not point toward dose-dependent risks for percentage of wine and AUD, we find it more likely and plausible that lifestyle factors and personal characteristics determine an individual's beverage preferences and the likelihood of later development of AUD.

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Paper III

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Comorbidity and temporal ordering of alcohol use disorders and other psychiatric disorders: results from a Danish register-based study

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Abstract

Background: Understanding the comorbidity of alcohol use disorders (AUD) and other psychiatric disorders may have important implications for treatment and preventive interventions. However, information on the epidemiology of this comorbidity is lacking. The objective of this study was to present results on lifetime psychiatric comorbidity of AUD in a large Danish community population.
Methods: A prospective cohort study was used, comprising 3 updated measures of sets of lifestyle covariates and 26 years of follow-up data on 18 146 individuals from the Copenhagen City Heart Study, Denmark. The study population was linked to national Danish hospital registers and a greater Copenhagen alcohol unit treatment register to detect registrations with AUD and other psychiatric disorders.
Results: Of the individuals invited to the study, 7.6% were registered with AUD, and among these, 50.3% had a lifetime comorbid psychiatric disorder. Personality disorders were the most common comorbid disorders (24%) together with mood disorders (16.8%) and drug abuse (16.6%). The risk of developing a psychiatric disorder in individuals who were already registered with AUD was larger than the risk of developing AUD in individuals who were already registered with another psychiatric disorder; these differences in risk were especially noticeable for anxiety disorders, personality disorders, and drug abuse.
Conclusions: AUD is frequently comorbid with other psychiatric disorders, and it is likely that AUD is both an etiologic factor in other mental disorders and a consequence of mental disease. However, in interpreting these complex and perhaps circular causal links, it is important to consider that AUD is registered before a comorbid psychiatric diagnosis more often than the reverse temporal order.

1. Introduction

Alcohol use disorders (AUD) are among the most prevalent psychiatric disorders in the general population [1,2]. Recognition of the prevalence of cooccurring psychiatric disorders with AUD has grown tremendously for the past 2 decades. A high prevalence of comorbid psychiatric disorders in individuals with AUD has been demonstrated in a number of large epidemiological studies [1-8], and it has been shown that AUD is more prevalent among people with psychiatric disorders than in the general population [9-12]. Alcohol use disorder is a highly prevalent disabling disorder that goes largely untreated [6], and individuals with AUD and comorbid psychiatric disorders are particularly at increased risk of both morbidity and mortality [13-20]. For example, a recent study demonstrated that depressed subjects with comorbid alcoholism were more likely to report a history of suicide attempts compared with depressed subjects without a history of alcoholism [21].

Studies examining both the comorbidity and the temporal ordering of AUD and psychiatric disorders in the general population are lacking, and this represents a major gap in our

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understanding of these disorders. This limits the development and testing of hypotheses that can be used to uncover etiologic factors and pathways underlying theses disorders. The aim of the present study was to address the question of comorbidity in a large population sample using Danish hospital and treatment registers.

1.1. Objectives of the study

The aims of the current study were to provide descriptive statistics on the prevalence of comorbid AUD and other categories of psychiatric disorders, to estimate hazard ratios (HRs) of developing AUD according to different categories of psychiatric disorders, and to estimate the HRs of developing psychiatric disorders according to AUD.

2. Materials and methods

2.1. Study population

Data from the Copenhagen City Heart Study (CCHS) [22,23] were used. The CCHS is an ongoing series of studies initiated in 1976. An age-stratified sample of 19 698 men and women aged 20 to 93 years who lived in the Copenhagen area was randomly drawn from the Central Population Register using the unique person identification number. In 1976 to 1978, they were invited by letter to answer a self-administered questionnaire, and 14 223 respondents returned the questionnaire, corresponding to 74% of the invited individuals. In the 1981 to 1983 follow-up (CCHS-II), all the previously invited, in addition to 500 new participants, were enrolled (response rate, 70%), and in the 1991 to 1993 follow-up (CCHS-III), nearly 3000 new participants were enrolled (response rate, 61%). Detailed descriptions of the study have been published elsewhere [22,23]. The Danish ethics committee for the City of Copenhagen and Frederiksberg approved the study (no. 01-144/01). All participants gave written informed consent.

2.2. Alcohol use disorders

By means of the unique person identification number, the study population was linked to 3 different registers to determine AUD: the *Danish Hospital Discharge Register* [24] containing information on all admissions to Danish hospitals since 1976, the *Danish Psychiatric Central Register* [25] containing records of all individuals who have been admitted to a psychiatric hospital in Denmark since 1969, and the *WINALCO database* [26] containing records of all individuals treated for alcohol problems in the Alcohol Unit, Hvidovre Hospital, Copenhagen, Denmark—an outpatient clinic for alcoholics covering the greater Copenhagen and Frederiksberg municipalities since 1954. Diagnoses are in the registers classified according to *International Classification of Diseases* (ICD), using the 8th revision until 1994 and the 10th revision from 1994 and onward. Individuals who had been given an ICD diagnosis of AUD in either the Danish Psychiatric Central Register or Danish Hospital Discharge Register and individuals who

Table 1
Characteristics of the 1756 individuals with alcohol use disorders (AUD)

	No. (%)	Average time between diagnoses (y)	Median time between diagnoses (y)	Range of time between diagnoses (y)
Mood disorders	295 (16.8)			
AUD before mood disorder	124 (42.0% of cases)	9.3	7.4	1.0-37.6
Mood disorder before AUD	76 (25.8% of cases)	8.0	5.1	1.1-32.3
Both diagnoses registered within a year	95 (32.2% of cases)	–	–	–
Psychotic disorders	145 (8.3)			
AUD before psychotic disorder	69 (47.6% of cases)	11.1	9.7	1-32.4
Psychotic disorder before AUD	43 (29.7% of cases)	10.0	8.4	1-24.5
Both diagnoses registered within a year	33 (22.8% of cases)	–	–	–
Anxiety disorders	116 (6.6)			
AUD before anxiety disorder	66 (56.9% of cases)	11.2	10.2	1.1-37.6
Anxiety disorder before AUD	28 (24.1% of cases)	7.3	4.4	1.1-32.5
Both diagnoses registered within a year	22 (19.0% of cases)	–	–	–
Personality disorders	422 (24.0)			
AUD before personality disorder	130 (30.8% of cases)	5.5	3.1	1.0-21.9
Personality disorder before AUD	79 (18.7% of cases)	8.4	6.4	1.1-27.2
Both diagnoses registered within a year	213 (50.5% of cases)	–	–	–
Drug abuse	291 (16.6)			
AUD before drug abuse	124 (42.6% of cases)	8.2	6.1	1.0-33.4
Drug abuse before AUD	42 (14.4% of cases)	9.3	5.2	1.2-32.3
Both diagnoses registered within a year	125 (43.0% of cases)	–	–	–
Any psychiatric disorder (other than AUD)	884 (50.3)			
AUD before psychiatric disorder	250 (28.3% of cases)	7.6	4.9	1.0-37.6
Psychiatric disorder before AUD	244 (27.6% of cases)	8.5	6.2	1.0-32.5
Both diagnoses registered within a year	390 (44.1% of cases)			

Table 2
Risk of AUD for individuals with psychiatric disorders (reference group is individuals without the concerned disorder)

Disorder	HR unadjusted (95% confidence interval)	HR adjusted[a] (95% confidence interval)	HR adjusted[b] (95% confidence interval)
Mood disorder	3.80 (2.78-5.19)	4.78 (3.50-6.56)	4.49 (3.26-6.15)
Psychotic disorder	3.31 (2.12-5.17)	3.74 (2.39-5.84)	3.17 (2.02-4.99)
Anxiety disorder	2.97 (1.71-5.14)	3.93 (2.27-6.83)	3.35 (1.93-5.83)
Personality disorder	3.92 (2.81-5.48)	4.73 (3.38-6.61)	4.28 (3.05-6.00)
Drug abuse	4.76 (2.85-7.94)	6.33 (3.78-10.59)	5.10 (3.04-8.55)
Any psychiatric disorder (except for AUD)	5.25 (4.25-6.49)	6.57 (5.30-8.14)	5.99 (4.82-7.44)

If the 2 disorders were registered within 1 year, the observation was deleted.
[a] Adjusted for sex.
[b] Adjusted for sex, smoking, cohabitation status, and educational level.

were registered in the WINALCO database were considered to have an AUD at the time of registration. In this study, AUD comprised the following ICD-8 and ICD-10 diagnoses: ICD-8 (303.09, 303.19, 303.20, 303.28, 303.29, 303.90, 303.91, and 303.99) and ICD-10 (F10.1 and F10.2).

2.3. Lifetime psychiatric diagnoses

Psychiatric diagnoses from all admissions to Danish hospitals were obtainable in either the Danish Hospital Discharge Register [24] or the Danish Psychiatric Central Register [25]. The following diagnostic categories were considered:

psychotic disorders: *ICD-8* (295, 297, 298.1-9, 299), *ICD-10* (F20-29)
mood disorders: *ICD-8* (296, 300.4, 298.0), *ICD-10* (F30-34, 38, 39)
anxiety disorders: *ICD-8* (300.0, 300.2, 300.3), *ICD-10* (F40-43)
personality disorders: *ICD-8* (301), *ICD-10* (F60)
drug abuse: *ICD-8* (304), *ICD-10* (F11-19—for only harmful use and dependence)
any psychiatric disorder, except for AUD: *ICD-8* (28, 30, 31), *ICD-10* (F1, F2, F3, F4, F5, F6, F7, F8, F9), minus AUD diagnoses.

Alcohol use disorders and the other psychiatric disorders were considered to have appeared simultaneously if both diagnoses were registered within the same year. Observations of this type were excluded from the Cox regression analyses.

2.4. Lifestyle covariates

Several lifestyle covariates were considered putative confounders in the association between AUD and other psychiatric disorders. The following were available in all 3 data collection follow-ups: *sex*, *smoking* (current smoker, previous smoker, and never smoker), *cohabitation status* (living alone, living with someone), and *educational level* (<8 years, 8-12 years, and >12 years).

2.5. Statistical analyses

As described above, the purpose of the analyses was to estimate the HRs of developing AUD according to different categories of psychiatric disorder and to estimate the HRs of developing different psychiatric disorder according to AUD. Because the focus was on onset of disorders, only first-time registrations of each disorder were used in the analyses. Data were analyzed by means of multiple Cox regression analysis, and by including age as the time variable, the estimates were adjusted for confounding by age. Subjects were followed from their date of entry, when they answered their first questionnaire between 1976 and 1993, to the date of the first registration of the outcome disorder, death, disappearance, or emigration or until the end of follow-up (January 2002)—whichever occurred first.

In contrast to time-fixed covariates, all our *psychiatric exposure covariates* in this study were time dependent because they were measured repeatedly over time, with the number of observations and the time between the observations varying between subjects. For all psychiatric disorders, we defined the time of exposure to begin from the exact date of the first diagnosis. Individuals registered with the outcome disorder before entry into the study were eliminated from the analyses, and to avoid misclassification of psychiatric disorders in the last years of follow-up, the end of follow-up was chosen to be the date where the first register (the Danish Psychiatric Central Register) ended its update.

To apply a Cox proportional hazards model with the time-dependent *lifestyle covariates* that were measured at regular

Table 3
Risk of psychiatric disorders for individuals with AUD (reference group is individuals without AUD)

Disorder	HR unadjusted (95% confidence interval)	HR adjusted[a] (95% confidence interval)	HR adjusted[b] (95% confidence interval)
Mood disorder	4.22 (3.21-5.55)	4.94 (3.74-6.52)	4.79 (3.61-6.36)
Psychotic disorder	4.80 (3.25-7.09)	5.17 (3.47-7.69)	4.51 (3.00-6.78)
Anxiety disorder	5.07 (3.53-7.27)	6.31 (4.37-9.11)	6.41 (4.40-9.36)
Personality disorder	7.29 (5.05-10.53)	9.19 (6.30-13.39)	8.09 (5.50-11.89)
Drug abuse	19.06 (12.94-28.06)	21.55 (14.42-32.21)	18.30 (12.05-27.78)
Any psychiatric disorder (except for AUD)	5.63 (4.56-6.94)	6.83 (5.50-8.48)	6.70 (5.38-8.34)

If the 2 disorders were registered within 1 year, the observation was deleted.
[a] Adjusted for sex.
[b] Adjusted for sex, smoking, cohabitation status, and educational level.

intervals in 1976 to 1978, 1981 to 1983, and 1991 to 1993, we prospectively assessed the risk of outcome in between examination increments based on determinations of lifestyle covariates derived from the preceding questionnaire. In case of missing data about smoking or education, the last observation was carried forward to maintain a large study population. Cohabitation status was the only factor not carried forward because we did not consider it reasonable to assume this to be a constant factor.

An overview of lifetime psychiatric disorders for individuals with AUD is shown in Table 1, including not only participants but also *all invited* individuals. Hazard ratios for AUD were computed for different groups of psychiatric disorders adjusted for (1) no covariates; (2) sex; and (3) sex, smoking, cohabitation status, and educational level (Table 2). Hazard ratios for the different groups of psychiatric disorders were computed according to AUD (Table 3), adjusted for the same covariates as in Table 2. All statistical analyses were done by means of the statistical software package SAS 9.1 (SAS, Cary, NC).

3. Results

Of the 23 189 individuals invited to the study, 1756 persons (7.6%) were registered at least once with AUD. Of the 18 146 respondents that completed a minimum of one questionnaire, 1200 persons (6.6%) were registered with AUD. Personality disorders were the most common comorbid disorders because 24.0% of all individuals with a lifetime diagnosis of AUD were also registered with a lifetime diagnosis of a personality disorder. Mood disorders and drug abuse were registered in 16.8% and 16.6%, respectively, of all individuals with AUD. Psychiatric disorders, other than AUD, were registered in 9.2% of the population without AUD (data not shown) and in 50.3% of the population with AUD (Table 1).

3.1. Descriptive results of comorbidity

Descriptive characteristics of the temporal ordering of AUD and the 6 categories of other psychiatric diagnoses are shown in Table 1. The category of personality disorders was the one with most cases registered within the same year of AUD (50.5%), whereas the category of anxiety disorders was the one least frequently registered within the same year as AUD (19.0%). Anxiety disorder was the diagnosis most frequently registered later than AUD (56.9%), whereas drug abuse was the least frequently registered diagnosis before AUD (14.4%). The average and medium times between diagnoses showed that personality disorders were generally registered closest in time to AUD compared with the other disorders. The lifetime prevalence of psychiatric disorders for individuals with AUD was 50.3%, and the average time span between AUD and any other psychiatric disorder was 7.6 to 8.5 years with a medium time between 4.9 and 6.2 years.

3.2. Risk of AUD according to other psychiatric disorders

Results of Cox regression models predicting secondary AUD are shown in Table 2. As described, these analyses were conducted after excluding observations with AUD and the psychiatric disorder in question registered within the same year. For all categories of psychiatric disorders, the risk of AUD was significantly increased. Drug abuse was associated with the highest risk of AUD with an adjusted HR of 5.10 (3.04-8.55) followed by mood disorders and personality disorders. All covariates included in the model were significant, except for educational level. Hence, men, smokers, and individuals living alone were at significantly increased risk of developing AUD. This was the case for analyses of all 6 diagnostic categories.

3.3. Risk of psychiatric disorders according to AUD

Table 3 shows that individuals with AUD were at increased risk of later developing mood disorders, psychotic disorders, anxiety disorders, personality disorders, drug abuse, and any other psychiatric disorder compared with individuals without AUD (Table 3). AUD showed the strongest association with drug abuse (adjusted HR = 18.30), personality disorders (adjusted HR = 8.09), and anxiety disorders (adjusted HR = 6.41). The risk of later being registered with any other psychiatric disorder was 6.70 for individuals with AUD. Sex was a significant confounding factor in both Tables 2 and 3. However, although Table 2 showed an increased risk among men compared with women, Table 3 showed an increased risk among women. The significance of each covariate varied with every psychiatric disorder. With all covariates into the same model, the risk of mood disorders was significantly affected by sex, smoking, cohabitation status, and educational level. For psychotic disorders, however, only cohabitation status was significant, and for personality disorders, only sex and smoking were significant factors.

4. Discussion

To our knowledge, this is the first study to investigate psychiatric comorbidity and temporal ordering of AUD in a large-scale register-based epidemiologic study. We found a lifetime prevalence of AUD of 7.6% among the invited study population as well as high incidences of comorbid mood disorders, psychotic disorders, anxiety disorders, personality disorders, and drug abuse. Among individuals with lifetime AUD, 50.3% had a lifetime comorbid psychiatric disorder. First-time AUD registration was most likely to precede first-time registration of mood disorders, psychotic disorders, anxiety disorders, personality disorders, and drug abuse in individuals with comorbid psychiatric disorders to AUD. Analyzing the risks over time, we found that the risk of developing a psychiatric disorder in individuals who were already registered with AUD was larger than the risk of

developing AUD in individuals who were already registered with another psychiatric disorder—these differences in risk were especially noticeable for anxiety disorders, personality disorders, and drug abuse.

4.1. Comparison with other studies

Prevalence and comorbidity rates vary substantially among studies in the literature, primarily because of methodological issues and large differences between clinical and population samples. The present study is intermediate between population studies screening for psychiatric disorders and clinical studies examining hospitalized patients. The first type of study would most likely find lower comorbidity rates than the present study, whereas the second type would most likely find higher comorbidity rates due to multiple diagnoses in hospitalized patients.

Results from the Epidemiologic Catchment Area (ECA) Study found that among those with an alcohol disorder, 37% had a comorbid mental disorder [4], whereas we, in this study, found a prevalence of 50.3% among individuals with AUD. Based on register data, a lifetime prevalence of AUD of 7.6% was observed in our study, whereas studies from around the world based on interviews and using *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, criteria have found a lifetime prevalence of AUD between 8.5% and 32.8% [2,27-30]. As in previous studies [2,27,31], men were at greater risk of AUD than women.

We found that 16.8% of individuals with lifetime AUD also had lifetime *mood disorder*, which is substantially lower than other studies based on clinical samples showing a lifetime prevalence of depression of 43.7% [32] and 42.2% [33] in treatment-seeking alcoholics. Taken together, previous studies suggest that there is a 2- to 4-fold increase in risk of the occurrence of either AUD or depression given the presence of 1 of the 2 disorders [34], corroborating our findings of HRs in the range 3.8 to 4.2. The comorbidity rate of *psychotic disorders* and AUD has been primarily investigated among patients with schizophrenia. Substance use disorders are very frequent, and clinically significant comorbidities in patients with schizophrenia and alcohol and nicotine are the most common substances of abuse [35]. The ECA study found that 33.7% of individuals with a diagnosis of schizophrenia or schizophreniform disorder also met the criteria for an AUD diagnosis at some point in life [4].

While 6.6% of individuals with AUD in this study also had a lifetime prevalence of *anxiety disorders*, results from the National Epidemiologic Survey on Alcohol and Related conditions found a 12-month prevalence of 33% among treatment-seeking alcoholics [1]. A *personality disorder* was the most common comorbidity disorder in this study as 24.0% of individuals with AUD had a personality disorder. Results from the National Epidemiologic Survey on Alcohol and Related conditions found that 28.6% of individuals with AUD had a personality disorder [36]. The differences in temporal ordering between AUD and other psychiatric disorders became especially clear for *drug abuse* because drug abusers had a risk of 4.8 of developing AUD, whereas people with AUD had a risk as large as 19.1 of developing drug abuse. Results based on the National Epidemiologic Survey on Alcohol and Related conditions found the adjusted odds ratio of lifetime AUD and drug abuse to be 10.4 when having one of the disorders [6], whereas results from the ECA Study found that the odds of having drug abuse or AUD when having 1 of the 2 disorders were 7 times greater than in the rest of the population [4].

Only a few studies have investigated the importance of temporal ordering in relation to AUD and psychiatric comorbidity. However, a study from the ECA community survey found that within 1 year, the risk of depression after onset of alcoholism was higher than the risk of alcoholism after depression [34]. Results from the National Comorbidity Survey showed that primary alcohol dependence was more common than primary depression among subjects with both disorders [3]. These findings are consistent with our results showing that the risk of developing mood disorders after the onset of AUD is higher than the risk of developing AUD after onset of mood disorders. A retrospective study found that roughly 3 of l0 comorbid patients abused alcohol or illicit drugs before the first signs of schizophrenia emerge, whereas the rest initiated substance abuse around or after the first signs [37]. In the present study, 48% of individuals with comorbid psychotic disorders and AUD were registered with AUD first.

4.2. Does the temporal ordering in this study reflect causality of the comorbidity?

Because this study is register based, the onset of AUD and other psychiatric disorders was based on when the individual appeared in the registry, which is when the individual entered the hospital or treatment facility. It is however quite likely that the disorder developed months or years before the individual entered treatment, wherefore the time of onset of the disorders is not accurate. In addition, the registration of a diagnosis depends not only on time of admission or contact with a hospital or an outpatient clinic but also on diagnostic practice and Danish diagnostic tradition; for example, with respect to schizophrenia, Danish diagnostic strategy has been conservative [38], and this may partly explain why AUD is usually diagnosed before this disease. On the other hand, it is possible that personality disorders are more often diagnosed close to the AUD diagnosis because AUD is often assumed to reflect a personality disorder.

Whether the temporal orderings of comorbid disorders in this study are in fact expressions of causality may differ for each pair of AUD and psychiatric disorder. It should, however, be born in mind that the etiology of both AUD and other mental disorders is complex with many contributing factors, and it is unlikely that AUD is ever a necessary and sufficient condition for the development of any other mental disorder. The cooccurrence of AUD and a mental disorder

may reflect 3 different scenarios: (1) AUD contributes to the development of the disorder, (2) the disorder contributes to the development of AUD, and (3) the development of both AUD and the disorder reflects common etiologic factors, including genetic predisposition and environmental influences such as childhood abuse or neglect. For most mental disorders, all 3 scenarios are likely, and in addition, the diagnosis of AUD, or a mental disorder may affect the likelihood of registration with other diagnoses.

Table 1 shows that in 20% to 50% of the cases, both AUD and the mental disorder of interest are diagnosed within a year. These cases are likely to reflect common etiologic factors or a diagnostic practice that increases the likelihood of simultaneous registration of both disorders. (It is also possible that one of the disorders may be an immediate consequence of the other disorder). For the cases with clear temporal separation between the 2 registrations, it is an open question whether temporal ordering reflects the "natural history" of the 2 disorders, diagnostic practice, or the fact that the first registered disorder contributes to the development of the last registered disorder.

Our results suggest similar risk of becoming registered with a diagnosis of AUD or *mood disorders* for individuals already registered with the other diagnosis. The high incidence of mood disorders among individuals with AUD may reflect the depressive effects of alcohol [39,40] and the psychosocial consequences of problem drinking as well as the fact that individuals with mood disorders use alcohol to cope with depressive symptoms. In addition, alcohol dependence and depression tend to run in families [41], and a substantial part of this covariance probably reflects shared genes [42,43].

In diagnostic hierarchies, schizophrenia is usually at the top and AUD at the bottom, reflecting the assumption that AUD is secondary to schizophrenia [44]. Nevertheless, it has been proposed that neurobiological vulnerability may interact with alcohol use to precipitate the onset of *schizophrenia* [45]. This has been supported by studies indicating that substance abuse is associated with an earlier age at onset of schizophrenia [9,37], and in our study, 47.6% of individuals with AUD were diagnosed with AUD before they were diagnosed with a psychotic disorder, whereas only 29.7% were registered with the psychotic disorder first.

Alcohol use disorder was registered before *anxiety disorders* with a greater frequency than any other disorder because 56.9% of individuals with AUD were registered with AUD before they were registered with anxiety disorders. In addition, the risk of developing anxiety disorders when registered with AUD (Table 3) was considerably larger than the risk of developing AUD when registered with an anxiety disorder (Table 2). This, however, may reflect the fact that people with anxiety disorders were less likely to be treated and registered unless comorbid disorders were present. Anxiety and depressive symptoms are very common in the general population [46,47], and alcohol abuse may also be symptomatically reflecting attempts to cope with anxiety, influencing the likelihood of being diagnosed with anxiety disorder.

Of individuals with AUD, 24% had a *personality disorder*, and in more than 50% of the cases, the 2 disorders were registered within the same year. Tables 2 and 3 show that the risk of personality disorders for individuals with AUD is considerably higher than the risk of AUD for individuals with personality disorders. This pattern of risks may reflect the fact that AUD substantially influence the likelihood of getting a diagnosis of personality disorder. It should also be kept in mind that disorders of personality are usually without any clear point of onset and etiologically probably reflecting most of the factors that may influence personality development.

Having AUD is obviously an indication of susceptibility to abuse, and therefore, the substantial comorbidity between AUD and *drug abuse* is not surprising. Alcohol use disorder is much more common than drug abuse, and our results suggest that comorbid cases of AUD and drug abuse primarily consist of individuals who first develop alcohol abuse and later drug abuse. Because the differences in HRs in Table 2 and 3 are quite large, it seems reasonable to suggest that individuals with susceptibility to abuse are most likely to begin abusing alcohol before they abuse other substances.

4.3. Methodological issues

The advantages of this study are the prospective design, the large study population sample, a long follow-up time, register information on all psychiatric diagnoses, and several updated measures of lifestyle covariates. The follow-up time of 26 years means that registration of cases with AUD and other psychiatric disorders should be as complete as possible in a register-based study. The large study population allowed us to exclude observations from the survival analyses with AUD and the psychiatric disorder in question registered within the same year, thereby clarifying the temporal ordering. Although all Danish residents have equal access to hospitals and all treatments are free of charge, misclassification of psychiatric disorders is still plausible, because the study sample only included individuals diagnosed at a hospital (or at an outpatient clinic with AUD) and the study was based on clinical diagnoses.

Individuals with comorbid AUD may be more likely to receive treatment than individuals with no AUD and thereby become registered in a Danish hospital—or outpatient register. In addition to this bias, health professionals may be more likely to look for psychiatric disorders among individuals with AUD than among individuals admitted for other reasons. These factors will result in overestimation of AUD comorbidity rates among psychiatric patients, and possibly also a difference in comorbidity rates between treated and untreated individuals with AUD. Thus, a recent population-based study showed that, relative to alcoholic adults who did not have an emergency department visit or hospitalization, alcoholic adults with use of these services

had an increased prevalence of personality disorders, depression, and other drug use disorders [48], and other studies have found similar results [49]. The differences in comorbidity between treated and untreated individuals with AUD may be smaller in Denmark because more alcoholics are treated in a health care system free of charge. This hypothesis is supported by the fact that our prevalence rates of psychiatric disorders in individuals with AUD are a great deal lower than the rates found in many other studies (as illustrated in the previous section). This suggests that we were able to capture not only the comorbid cases of AUD but rather a more wide-ranged sample of individuals with AUD.

4.4. Implications

From this study as well as previous studies, it seems that comorbidity of AUD is the rule rather than the exception. Understanding more about how different disorders cooccur may provide important opportunities for prevention.

Patients with comorbid AUD often have a poorer treatment response and a worse course of illness over time [50]. Thus, patients with schizophrenia with comorbid substance disorders have been shown to be highly prone to increased symptom severity, increased rates of hospitalization, violence, victimization, no adherence to medication, and poor overall response to pharmacologic treatment compared with those without comorbid addiction [9]. Similarly, patients with bipolar disorder and alcoholism have been found to have more hospital admissions [51] and a poorer clinical course [52] than bipolar patients without alcoholism. Comorbid disorders to AUD may also have important impact on the treatment of AUD; for example, a study of treatment-seeking substance-dependent patients found that patients with relapse more frequently had major depression and agoraphobia [53].

It has previously been shown that remission of alcoholism increases the remission of depression [54,55] and also that the course of illness among subjects hospitalized for comorbid depression and alcoholism was different in those with primary depression vs those with primary alcoholism [56]. It is reasonable to assume that the possible etiological role of comorbid AUD has important implications for treatment of most psychiatric disorders, but even in cases with no causal relationship between AUD and another mental disorder, the cooccurrence of AUD may worsen the symptoms and negatively influence the course of the other disorder.

Although our results suggest that the risk of a psychiatric disorder for individuals with AUD is larger than the risk of AUD for individuals with psychiatric disorders, both the observed risk patterns and the discussion above indicate that it is difficult to evaluate the significance of temporal ordering in an etiologic perspective. However, we believe that descriptions and etiologic interpretations of the relationships between AUD and other psychiatric disorders should consider the temporal ordering of the disorders and the risk of psychiatric disorders associated with AUD.

Understanding the comorbidity between AUD and other psychiatric disorders may have important implications for treatment and preventive interventions. The observed substantial comorbidity underlines the need for intervention aiming to reduce self-medication with alcohol in psychiatric patients and the need to conduct a thorough psychopathological evaluation of individuals with AUD. Furthermore, the results emphasize the importance of ongoing development of improved treatments for those individuals meeting criteria for both AUD and other psychiatric disorders.

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Paper IV

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Alcohol use disorders increase the risk of completed suicide — Irrespective of other psychiatric disorders. A longitudinal cohort study

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Abstract

Knowledge of the epidemiology of suicide is a necessary prerequisite for developing prevention programs. The aim of this study was to analyze the risk of completed suicide among individuals with alcohol use disorders (AUD), and to assess the role of other psychiatric disorders in this association. A prospective cohort study was used, containing three updated sets of lifestyle covariates and 26 years follow-up of 18,146 individuals between 20 and 93 years of age from the Copenhagen City Heart Study in Denmark. The study population was linked to four different registers in order to detect: Completed suicide, AUD, Psychotic disorders, Anxiety disorders, Mood disorders, Personality disorders, Drug abuse, and Other psychiatric disorders. Individuals registered with AUD were at significantly increased risk of committing suicide, with a crude hazard ratio (HR) of 7.98 [Confidence interval (CI): 5.27–12.07] compared to individuals without AUD. Adjusting for all psychiatric disorders the risk fell to 3.23 (CI: 1.96–5.33). In the stratified sub-sample of individuals without psychiatric disorders, the risk of completed suicide was 9.69 (CI: 4.88–19.25) among individuals with AUD. The results indicate that individuals registered with AUD are at highly increased risk of completed suicide, and that registered co-morbid psychiatric disorders are neither sufficient nor necessary causes in this association.

Keywords: Epidemiology; Psychotic disorders; Anxiety disorders; Mood disorders; Personality disorders; Drug abuse; Prospective study

1. Introduction

Globally, suicide rates have increased by 60% over the past 45 years and in 1998 suicide was estimated to represent 1.8% of the total burden of disease (World Health Organization, 2005). In 2001 the World Health

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Organization reported that self-inflicted injuries including suicide accounted for more than 800,000 deaths worldwide per year (World Health Organization, 2001), and in the United States alone, there are approximately 30,000 completed suicides per year (Sher, 2004). The Danish national suicide rate has been decreasing, though, over the past two decades, with the rate being 16.6 per 100,000 in 2001 (Christiansen and Jensen, 2007).

Evidence linking alcohol use and suicidal behavior has been reported in the literature for several decades (Bernal et al., 2007; Conner and Duberstein, 2004; Murphy and Wetzel, 1990; Roy and Linnoila, 1986). However, since data on nonfatal suicidal behaviors are more readily available than data on completed suicide, most studies on suicide among people with alcohol problems have focused upon suicidal ideation or attempted suicide. The distinction between attempted and completed suicide is important due to demographic, personality and clinical dissimilarities (Conner and Duberstein, 2004) and more studies are needed to unravel risk factors of completed suicide.

Suicide is most frequently considered to be a complication of a psychiatric disorder (Christiansen and Jensen, 2007; Bernal et al., 2007), and research has documented that major depressive episodes (Bernal et al., 2007; Moller, 2003), affective disorders (Allgulander et al., 1992; Moller, 2003), anxiety disorders (Sareen et al., 2005), and schizophrenia and other psychoses (Allebeck and Allgulander, 1990b; Allgulander et al., 1992) are independent risk factors for suicidal behavior. Furthermore, large epidemiological studies have shown that comorbid psychiatric disorders are frequent in patients with alcohol use disorders (AUD) (Kessler et al., 1997; Regier et al., 1990). However, to our knowledge, the potential confounding effect of psychiatric disorders upon the association between AUD and completed suicide is unknown.

The high incidence worldwide of AUD, the high prevalence of suicides in this population, and the consequences for individuals, families, and society are all factors indicating the need for more research. The availability of a 26-year follow-up study of a large population sample (Appleyard et al., 1989; Schnohr et al., 2001) together with the data from four Danish registers provided us with a unique opportunity to assess the association between AUD and completed suicide as well as to adjust for both lifestyle factors and psychiatric disorders. Our hypothesis was that individuals with AUD were at increased risk of committing suicide — irrespective of the presence of other psychiatric disorders.

2. Methods

2.1. Study population

Data from the Copenhagen City Heart Study (CCHS) were used (Appleyard et al., 1989; Schnohr et al., 2001). The CCHS is an ongoing series of studies conducted in the Danish population, initiated in 1976. An age-stratified sample of 19,698 men and women aged 20 to 93 years who lived in the Copenhagen area were randomly drawn from the Central Population Register, using the unique person identification number and invited by letter to answer self-administered questionnaires in 1976–78, where 14,223 respondents returned the questionnaire, corresponding to 74% of the invited individuals. In the 1981–83 follow-up (CCHS-II), the study population was supplemented with 500 new participants aged 20–29 years and nearly 3000 new participants were enrolled in the 1991–93 follow-up (CCHS III). Detailed descriptions of the study have been published elsewhere (Appleyard et al., 1989; Schnohr et al., 2001).

2.2. Suicide

All Danish residents who die in Denmark are recorded in the Danish Causes of Death Register (Juel and Helweg-Larsen, 1999), using the World Health Organization's International Classification of Diseases (ICD) to classify cause of death. Individuals invited to participate in the CCHS were linked to this register, using person identification numbers, in order to determine completed suicide. The database contains causes of death until March 2004. Classifications used to define completed suicide were in the subdivisions of "Suicide and self-inflicted injury" (ICD-8: E950–959) or "Intentional self-harm" (ICD-10: X60–84). Classifications in the subdivisions of "Injury undetermined whether accidentally or purposely inflicted" (ICD-8) and "Event of undetermined intent" (ICD-10) were *not* defined as completed suicides in this study.

2.3. Alcohol use disorders

The study population was linked to three different registers in order to determine alcohol use disorders: The *Danish Hospital Discharge Register* (Jurgensen et al., 1986) contains information on all admissions to Danish hospitals since 1976; the *Danish Psychiatric Central Register* (Munk-Jorgensen and Mortensen, 1997) contains records of all individuals that have been admitted to a psychiatric hospital in Denmark since 1969; and the

WINALCO-database (Becker, 2004) contains records of all individuals treated for alcohol problems in the Alcohol Unit, Hvidovre Hospital — an outpatient clinic for alcoholics covering the greater Copenhagen and Frederiksberg municipalities since 1954. Diagnoses in the registers are classified according to ICD, using the eighth revision until 1994 and the tenth revision from 1994 and onward. Individuals registered with an ICD of AUD in either the Danish Psychiatric Central Register or the Danish Hospital Discharge Register and individuals who were registered in the WINALCO-database were considered to have an AUD at the given time. In this study, AUD comprised the following diagnoses: ICD-8 (303.09; 303.19; 303.20; 303.28; 303.29; 303.90; 303.91; and 303.99) and ICD-10 (F10.1; F10.2).

2.4. Lifetime psychiatric diagnoses

All psychiatric admissions to Danish hospitals were obtainable in either the Danish Hospital Discharge Register (Jurgensen et al., 1986) or the Danish Psychiatric Central Register (Munk-Jorgensen and Mortensen, 1997). The following diagnostic categories were included as putative confounders in the analyses:

- Psychotic disorders: ICD-8 (295, 297, 298.1–9) and ICD-10 (F20–29)
- Anxiety disorders: ICD-8 (300.0, 300.2, 300.3) ICD-10 (F40–43)
- Mood disorders: ICD-8 (296, 300.4, 298.0) ICD-10 (F30–34, 38, 39)
- Personality disorders: ICD-8 (301) ICD-10 (F60)
- Drug abuse: ICD-8 (304) ICD-10 (F11–19 — for only points 1 and points 2)
- Other disorders: All other psychiatric diagnoses than those mentioned above, except from substance-induced disorders and organic mental disorders.
- All psychiatric disorders: All of the above mentioned categories.

2.5. Life style characteristics

Several lifestyle factors were considered putative confounders in the association between AUD and suicide. The following variables were available from all three data-collection follow-ups: *Sex, Education* (less than 8 years, 8–12 years, and more than 12 years), *Income* (three monthly income groups: low, middle, and high, *Cohabitation status* (living alone, living with someone), *Marital status* (not currently married, currently married), *Divorce history* (never divorced, divorced), *Smoking* (current smoker, previous smoker, and never smoker), *Physical exercise in leisure time* (less than 2 h/week, 2–4 h/week, more than 4 h/week.

2.6. Statistical analyses

The purpose of the analyses was to estimate the risk of suicide among individuals with AUD. Data were analyzed by means of multiple Cox Regression analysis and by including age as the time variable the estimates were adjusted for confounding by age. Subjects were followed from their date of entry, when they received the questionnaire between 1976–93, to the date of suicide, death from other causes, disappearance, or emigration or until the end of follow-up (January 2002) — whichever occurred first.

In contrast to time-fixed covariates, all covariates in this study were time-dependent as they were measured repeatedly over time, with the number of observations and the time between the observations varying between subjects. For AUD and other psychiatric disorders, we defined the time of exposure to begin from the exact date of the first diagnosis. In order to avoid misclassification of AUD in the last years of follow-up, the end of follow-up was chosen to be the date where the first register (the Danish Psychiatric Central Register) ended its update. Data were reorganized in stacked risk sets to apply a Cox proportional hazards model with the time-dependent lifestyle covariates that were measured in 1976–78, 1981–83, and 1991–1993. At each event time, the patients at risk and the recent values of the time-dependent covariates were determined. These risk sets were stacked into one large data set and analyzed using Cox regression. In case of missing data about education, income, smoking, or physical exercise the last observation was carried forward to maintain a large study population. Cohabitation status, marital status, and divorce history were, as the only factors, not carried forward as we did not consider it rational to assume these to be constant factors. Analyses based only on register information included all invited individuals, while analyses including lifestyle covariates were based on the sub-sample who responded to at least one questionnaire.

Baseline characteristics for subjects who entered the study at the first examination in 1976–78 are shown in relation to completed suicide (Table 1) with chi-square tests. An overview of lifetime psychiatric disorders in relation to completed suicide is shown for the invited study population (Table 2). In order to investigate the effect of each possible confounder upon the time to completed suicide, hazard ratios were computed separately for each (Table 3). Next, hazard ratios were computed according to AUD, adjusted for: 1) No covariates, 2) Sex, 3) Lifestyle covariates 4) Psychotic disorders, 5) Anxiety disorders, 6)

Table 1
Baseline lifestyle characteristics (1976–78) in relation to completed suicide.

	Non suicide completers		Suicide completers		*df*	χ^2	*P*
	N	%	*N*	%			
Proportion	14,111	99.2	112	0.79	–	–	–
Proportion men	6451	45.7	60	53.6	1	3.66	0.056
Education, highest	1621	11.5	23	20.5	2	9.67	0.008
Income % lowest	3776	27.8	36	33.0	2	1.62	0.444
Living alone	3789	26.9	42	37.5	1	6.36	0.012
Currently married	9311	66.1	59	52.7	1	8.87	0.003
Had a divorce	1394	9.9	18	16.1	1	4.74	0.030
Current smoker	8935	63.3	84	75.0	2	6.59	0.037
Physical exercise, lowest	2807	19.9	31	27.7	2	4.44	0.109

Mood disorders, 7) Personality disorders, 8) Drug abuse, 9) All four psychiatric disorders, 10) Other psychiatric disorders, 11) All psychiatric disorders (Table 4). The interaction between AUD and psychiatric disorders with respect to risk of suicide was tested. Based on the results the study population was stratified according to the presence or absence of other psychiatric disorders (Table 5). All statistical analyses were conducted using the statistical software package SAS 9.1.

3. Results

Of the 23,189 individuals invited to the study, 209 persons (0.90%) committed suicide, while 1756 persons (7.6%) were registered at least once with AUD. Psychiatric disorders, other than AUD, were registered in 9.2% of the population without AUD and in 50.3% of the population with AUD. 18,146 respondents completed at least one questionnaire and of these, 123 persons (0.68%) later committed suicide while 1200 persons (6.6%) were registered with AUD. Among the non-respondents, 1.71% committed suicide and 11.03% were registered with AUD. The mean age of individuals committing suicide was 59.8 years for women and 57.3 years for men, with ages ranging from 30 years to 93 years.

Table 2
Lifetime psychiatric disorders in relation to completed suicide for the entire invited study population.

	Non suicide completers (*N*=22,980)	Suicide completers (*N*=209)	*df*	χ^2	*P*
Proportion (%)	99.1	0.9	–	–	–
Alcohol use disorder (%)	7.4	27.3	1	116.9	<0.0001
Psychotic disorder (%)	2.5	10.5	1	53.0	<0.0001
Anxiety disorder (%)	1.8	5.3	1	13.5	0.0002
Mood disorder (%)	5.1	20.1	1	93.6	<0.0001
Personality disorder (%)	3.7	23.0	1	209.7	<0.0001
Drug abuse (%)	2.0	13.9	1	141.8	<0.0001
Other psychiatric disorders[a] (%)	3.6	13.9	1	60.3	<0.0001
Any psychiatric disorder except from AUD (%)	12.0	49.3	1	267.4	<0.0001

[a] Other than: Psychotic disorders, Anxiety disorders, Mood disorders, Personality disorders, Drug abuse.

3.1. Baseline characteristics of suicide completers

Chi-square tests of baseline characteristics in 1976–78 and completed suicide later on (Table 1) show that, compared with people who did not commit suicide,

Table 3
HRs for completed suicide according to updated putative confounders.

Putative confounders	Hazard ratio (95% confidence interval)
Women	1.00 (reference)
Men	1.70 (1.19–2.44)
Education up to 8 years	1.00 (reference)
Education 8–11 years	0.71 (0.47–1.07)
Education 12+ years	1.38 (0.84–2.25)
High income	1.00 (reference)
Middle income	1.35 (0.79–2.30)
Low income	2.18 (1.23–3.85)
Living with someone	1.00 (reference)
Living alone	1.36 (0.93–1.98)
Currently married	1.00 (reference)
Not currently married	1.45 (1.01–2.08)
Never divorced	1.00 (reference)
Divorced	1.43 (0.89–2.29)
Never smoker	1.00 (reference)
Previous smoker	1.08 (0.56–2.07)
Current smoker	1.87 (1.12–3.13)
Exercise, more than 4 h	1.00 (reference)
Exercise, 2–4 h	1.03(0.67–1.57)
Exercise, less than 2 h	1.77 (1.09–2.88)
No psychotic disorder	1.00 (reference)
Registered with psychotic disorder	7.89 (4.24–14.65)
No anxiety disorder	1.00 (reference)
Registered with anxiety disorder	7.69 (3.76–15.76)
No mood disorder	1.00 (reference)
Registered with mood disorder	11.34 (7.49–17.15)
No personality disorder	1.00 (reference)
Registered with personality disorder	9.01 (5.77–14.07)
No drug abuse	1.00 (reference)
Registered with drug abuse	10.78 (6.05–19.21)
No “other psychiatric disorder”	1.00 (reference)
Registered with “other psychiatric disorder”	11.79 (8.26–16.81)
No psychiatric disorder	1.00 (reference)
Registered with a psychiatric disorder (AUD not included)	12.87 (9.00–18.40)

Table 4
HRs for completed suicide according to alcohol use disorders.

Adjusted for	Hazard ratio	95% Confidence interval
Unadjusted	7.98	(5.27–12.07)
Sex	7.36	(4.82–11.23)
Lifestyle covariates [a]	5.91	(3.76–9.27)
Psychotic disorders	6.88	(4.48–10.55)
Anxiety disorders	7.17	(4.69–10.97)
Mood disorders	4.72	(2.99–7.44)
Personality disorders	4.54	(2.73–7.55)
Drug abuse	5.95	(3.71–9.56)
All five disorders [b]	3.44	(2.10–5.64)
Other psychiatric disorders [c]	6.02	(3.80–9.56)
All psychiatric disorders [d]	3.23	(1.96–5.33)

(Reference group is: individuals never registered with AUD).
[a] Adjusted for: Sex, Education, Income, Cohabitation status, Marital status, Divorce history, Smoking, and Physical exercise.
[b] Psychotic disorders, Anxiety disorders, Mood disorders, Personality disorders, Drug abuse.
[c] Other than: Psychotic disorders, Anxiety disorders, Mood disorders, Personality disorders, Drug abuse.
[d] Psychotic disorders, Anxiety disorders, Mood disorders, Personality disorders, Drug abuse, and "other psychiatric disorders".

suicide completers are more likely to: be men, have a low education, live alone, be unmarried, having had a divorce, and being a smoker. In addition, suicide completers were more likely to have had a lifetime psychiatric diagnosis: 49.3% were registered with a psychiatric diagnosis, other than AUD, at some point. AUD was registered in 27.3% of all suicide completers, personality disorders in 23.0%, and 20.1% of all suicide completers were registered with mood disorders (Table 2). The univariate analyses in Table 3 show the effect of each possible confounder upon the time of completed suicide taking place.

3.2. Risk of suicide for individuals with AUD

Subjects registered with AUD were at significantly higher risk of committing suicide (Table 4). The crude hazard ratio (HR) of completed suicide was 7.98 (95% CI 5.27–12.07) for subjects with AUD compared to subjects without AUD. Adjusting for sex, the risk diminished slightly, and adjusting for all lifestyle covariates available, the risk fell to 5.91 (95% CI 3.76–9.27). All five groups of psychiatric diagnoses were significant confounders in the association between AUD and completed suicide with the hazard ratio dropping down to 4.54 (95% CI 2.73–7.55) when adjusting for personality disorders (Table 4). Including all five groups of diagnoses in the model at the same time reduced the risk of completed suicide among individuals with AUD to 3.44 (95% CI 2.10–5.64), and with adjustment for all psychiatric disorders the risk fell to 3.23 (95% CI 1.96–5.33).

3.3. Stratifying by psychiatric disorders

Because of a significant interaction between AUD and psychiatric disorders ($P=0.0006$) with respect to risk of completed suicide (data not shown), the study population was stratified according to psychiatric disorders other than AUD. This analysis showed that the risk of completed suicide among individuals with AUD was substantially different in the two sub-samples (Table 5). Among people with psychiatric disorders, the risk of completed suicide was 2.21 (95% CI 1.29–3.80), while the risk among people without psychiatric disorders was 9.69 (95% CI 4.88–19.25) (Table 5). Lifestyle covariates reduced the HRs most in the sub-sample with no psychiatric disorders.

4. Discussion

Our results suggest that individuals registered with AUD are at increased risk of committing suicide, and that the risk continues to be significant after adjusting for all psychiatric disorders. We found a 7.98-fold elevated risk of completed suicide among individuals who had been registered with an AUD diagnosis compared to individuals, who were never registered with AUD. Adjusting for five categories of psychiatric disorders that are frequently co-morbid with AUD, the risk dropped to 3.44, and adjusting for all psychiatric disorders the risk fell to 3.23. Stratifying our study population according to psychiatric disorders we found a 9.29-fold risk of completed suicide among individuals with AUD in the sub-sample with no psychiatric disorders.

Table 5
HRs for completed suicide according to alcohol use disorders, stratified by presence of psychiatric disorders.

	Registered with a psychiatric disorder (other than AUD)			Never registered with a psychiatric disorder (other than AUD)		
	Unadjusted	Adjusted for sex	Adjusted for lifestyle covariates [a]	Unadjusted	Adjusted for sex	Adjusted for lifestyle covariates [a]
Registered with AUD	2.21 (1.29–3.80)	2.02 (1.16–3.53)	1.94 (1.08–3.49)	9.69 (4.88–19.25)	7.61 (3.77–15.37)	5.86 (2.83–12.15)

(Reference group is: individuals never registered with AUD).
[a] Adjusted for: Sex, Education, Income, Cohabitation status, Marital status, Divorce history, Smoking, and Physical exercise.

4.1. Comparison with other studies

The estimated hazard ratio of 7.98 for suicide among individuals with AUD is in accordance with the estimates given in a Norwegian study that examined risk of suicide among alcohol abusers in military conscripts and found a crude risk of 6.7 among male alcohol abusers (Rossow and Amundsen, 1995). In addition, our findings contribute to support findings from previous studies demonstrating higher suicide mortality among alcohol abusers (Murphy and Wetzel, 1990; Bernal et al., 2007; Roy and Linnoila, 1986) and higher prevalence of alcohol abusers among suicide victims in retrospective post-mortem studies (Conwell et al., 1996). We found that 49.3% of the 209 persons who committed suicide had been registered with a lifetime psychiatric diagnosis other than AUD, which is somewhat higher than a Swedish study that found a prevalence of only 44% (including AUD) among suicide completers (Allebeck and Allgulander, 1990a). In this study mood disorders and drug abuse were studied and found to be the strongest independent predictors of completed suicide with a more than 10-fold increased risk. This is in accordance with a Swedish study showing that the highest risk of completed suicide was found among individuals with affective disorders, unspecified psychoses, paranoid psychoses, addiction to prescription drugs, and schizophrenia (Allgulander et al., 1992). We found that male sex, low income, being unmarried, smoking, and low physical exercise were significant independent risk factors for completed suicide (Table 3). The findings are in agreement with previous studies investigating risk factors for both suicidal behavior and completed suicide (Agerbo et al., 2007; Bernal et al., 2007; Conner and Duberstein, 2004; Murphy et al., 1992). Especially the role of smoking has gained much attention in suicide research. In this study we found an unadjusted 1.87-fold increased risk of completed suicide among smokers, while other studies have found more than twofold elevated risk of suicide attempts among smokers after adjusting for psychiatric disorders (Riala et al., 2007).

4.2. AUD and suicide

There are several ways in which the positive association between AUD and completed suicide may be explained. Apparently, a large part of the association between AUD and suicide is explained by the co-morbidity of AUD and other psychiatric diseases — either by psychiatric disorders mediating the effect of AUD on suicide or by AUD being the consequence of the psychiatric disorder. However, the risk of suicide among individuals with AUD did not become insignificant after adjusting for all psychiatric diseases, and our stratified HR in Table 5 showed a 9.69-fold risk of suicide among individuals with AUD and no co-morbid psychiatric diseases. Therefore, some of the elevated risk may be attributed to a direct association between AUD and suicide. This could be explained by the fact that AUD often cause personal and social problems — factors that increase the risk of suicide. Moreover, suicide may be a direct consequence of a large alcohol intake creating a disinhibiting effect, which may increase the risk of suicidal behaviors; or be an indirect consequence of a long-lasting large alcohol intake, affecting mood and aggressive/impulsive traits and undermining social relationships or support, thereby increasing suicidal thoughts. It is, however, very likely, that AUD and suicide are manifestations of the same underlying traits that were not registered in this study. Based on a thorough review, a model of suicidal behavior among individuals with alcoholism has recently been proposed (Conner and Duberstein, 2004). Predisposing factors presumed to increase the risk of suicide were aggression/impulsivity and severity of alcoholism together with negative affect and hopelessness. Major depressive episodes and stressful life events – particularly interpersonal difficulties – were conceptualized as precipitating factors (Conner and Duberstein, 2004). Abnormal serotonergic function has been associated with suicidal behavior (Mann and Malone, 1997), aggression, and alcoholism (Mann, 1994), and it has been proposed that abnormal serotonergic activity to some extent mediates the genetic and developmental predispositions for suicide, aggression and alcoholism (Mann et al., 1999). Human and animal studies have indicated that serotonin abnormalities can result in increased disinhibitory psychopathology (indicative of suicide), impulsive aggression, alcoholism and drug abuse (Crabbe et al., 1996; Saudou et al., 1994; Mann et al., 2001). Our finding of elevated risk of completed suicide among cigarette smokers may also be related to serotonin dysfunction.

4.3. Methodological issues

The advantages of this study are the prospective design, the large study population, a long follow-up time, several updated measurements of lifestyle covariates, and register information on psychiatric diagnoses. Due to the prospective design, selection and recall bias was minimized, and 26 years follow-up time means that registration of cases with AUD and cases with completed suicide should be optimal for a register based study. In Denmark,

all residents have equal access to psychiatric hospitals and all treatments are free of charge. However, misclassification of psychiatric disorders is still plausible, as the registers only included diagnoses leading to hospital admission. Assuming that we only included the most severe cases of AUD in this study and assuming that there is a dose–response relationship between AUD and suicide, it is very likely that we would have found a weaker association between AUD and suicide if we had used a more comprehensive measure of AUD than registration at a hospital or an outpatient clinic.

Underestimation of the prevalence of completed suicides is possible, as the boundary between completed suicide and accidental death in some cases can be complex to determine thus leading to possible misclassification in the Danish Causes of Death Register. The diagnoses of death used in this study are all in the subcategories of "Suicide and self-inflicted injury" (ICD-8) or "Intentional self-harm" (ICD-10). However, diagnoses of "Injury undetermined whether accidentally or purposely inflicted" (ICD-8: E980–989) and "Event of undetermined intent" (ICD-10: Y10–Y34) were not defined as completed suicides in the study, and we might have lost cases that were wrongly diagnosed in these subcategories. However, such misclassification would probably lead to underestimation of the significance of our findings.

As register information was available also for non-respondents, we know that there was a higher percentage of both suicide and AUD among the non-respondents than among the respondents. In analyses where lifestyle covariates were included non-respondents were excluded. This may have affected our obtained hazard ratios, as there are reasons to believe that these non-respondents are different from the general population.

4.4. Generalization

The results are based only on individuals that were registered at a hospital or at an outpatient clinic and can possibly only be generalized to individuals with the most severe AUD and other psychiatric disorders. For these patients the presented results may largely be generalizable to the Danish population as well as other Western societies. Considerable speculations have been proposed concerning the effect of place of residence on suicide risk (Durkheim, 1952). The impact of AUD on suicide presumably varies with the prevalence of suicide and with cultural differences in drinking cultures, including societal reactions to AUD. However, a Danish study found that the variation in prevalence of suicide in different geographical areas could be explained by the proportion of high-risk individuals living in particular areas rather than the characteristics of the areas themselves (Agerbo et al., 2007). If these results apply to suicides in general, it suggests that our results can be generalized not only to the Danish population but that the enlarged risk of suicide among individuals with AUD exists in many societies.

5. Conclusion

We suggest that individuals registered with AUD are at increased risk of committing suicide irrespective of the presence of other psychiatric disorders. Although the risk decreased when adjusting for psychiatric disorders, the risk among individuals with AUD was still significantly elevated by more than 3 times that of individuals without AUD after adjusting for all psychiatric disorders. In addition, our stratified results showed that individuals with no co-morbid psychiatric disorder to their AUD had an increased risk of more than 9 times that of individuals with neither a psychiatric disorder nor AUD. Our results can only be generalized to cases of AUD resulting in hospital admissions, but we consider our findings to be of noteworthy importance due to the unique data material, capturing updated lifetime information on both lifestyle factors and psychiatric disorders from a large study population.

It is estimated that 50% of those who commit suicide had sought professional help within 1 month prior to the act (Isacsson et al., 1992). Our results emphasize the importance for professionals to treat AUD and to be especially aware of potential suicide ideation in this population — irrespective of occurrences of other psychiatric disorders. Clinicians should be aware that suicidal behavior is common in individuals with AUD and should evaluate all patients with AUD for suicide risk regardless of possible psychiatric co-morbidity.

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