

SCHOOL OF BUSINESS AND SOCIAL SCIENCES AARHUS UNIVERSITY

Complementary data sources: Using register and survey data to investigate alcohol-related harm

PhD dissertation

Julie Elizabeth Brummer

Aarhus BSS Aarhus University Centre for Alcohol and Drug Research Department of Psychology and Behavioural Sciences 2023



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Centre for Alcohol and Drug Research Department of Psychology and Behavioural Sciences School of Business and Social Sciences Aarhus University

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Handed in for assessment: 30 January 2023 Public defense: 16 May 2023

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ACKNOWLEDGMENTS

I would like to thank my main supervisor, Morten Hesse, for inspiring me with his insights, creativity, and enthusiasm and for his thoughtful advice at every step of the process. I am grateful to my co-supervisor, Kim Bloomfield, for sharing her vast knowledge of alcohol research, including me in her projects and network, and urging me to apply to the PhD program.

Thank you to Kate Karriker-Jaffe for hosting me during my research stay in California and providing valuable feedback on all of my manuscripts and to Ulrike Grittner for graciously and patiently answering my statistical questions. I'm very thankful for the help I've received during the last four years from Torsten Kolind, Abdu Kedir Seid, Michael Mulbjerg Pedersen, Margit Anne Petersen, Kristine Rømer Thomsen, Esben Houborg, Thomas Friis Søgaard, Lisa Schölin, Sidsel Schrøder, and Annette Bang Rasmussen.

Thank you to my fellow PhD students at the Centre for Alcohol and Drug Research for comments on my first paper and for endless support. I feel extremely fortunate to have been able to collaborate with Kirsten Søndergaard Frederiksen, who was always generous with her time and her good ideas. To my wonderful officemates, Priya Ranganath and Morgan Bancroft, I'm so glad to have shared this experience with you.

Lastly, I would like to thank my loving and supportive family. Thank you to Mikkel for listening to and discussing my research ideas (and problems), giving good advice, and encouraging me daily. To Teo and Loa, thank you for always lifting my spirits.

LIST OF STUDIES

This PhD thesis is based on the following three individual studies:

- Study 1 Brummer, J., Hesse, M., Frederiksen, K. S., Karriker-Jaffe, K. J., & Bloomfield, K. (2021). How do register-based studies contribute to our understanding of alcohol's harms to family members? A scoping review of relevant literature. *Journal of Studies on Alcohol and Drugs*, 82(4), 445–456.
- Study 2 Brummer, J., Bloomfield, K., Karriker-Jaffe, K. J., & Hesse, M. (2022).
 Hazardous drinking and violence-related hospitalizations in the Danish general population: A historical cohort study. *Drug and Alcohol Dependence*, 233, 109338.
- Study 3 Brummer, J., Bloomfield, K., Karriker-Jaffe, K. J., Pedersen, M.M. & Hesse, M. (2023). Using the Alcohol Use Disorders Identification Test to predict admission for alcohol-related conditions in the Danish general population: A record-linkage study. *Addiction (Abingdon, England)*, 118(1), 86–94.

OVERVIEW OF THE THESIS

This PhD thesis examines and demonstrates how register data can complement and inform survey-based measures of alcohol exposure and harm. The following table outlines the main methodological features and findings of the three independent studies that comprise the thesis:

| Study | Overview of research questions | Data and methods | Main findings |
|-------|--|---|--|
| 1 | What are the methodological features of existing register-based studies of alcohol's harms to family members? What are the main findings, and how do the findings differ from those of survey-based studies, if at all? What are the gaps in the literature? | Scoping review Search of PubMed/MEDLINE, EMBASE, and PsycINFO databases 5,961 records screened, 403 full-text articles assessed, and 91 studies included in final review | Register-based research on alcohol's harms to family members has largely drawn on hospital records to identify heavy drinkers and primarily focused on the parent-child relationship. Register-based studies show that children of heavy drinkers are at higher risk for mental disorders, disease and injury hospitalizations, infant and child mortality, criminality, poor employment and educational outcomes, abuse/neglect, and placement in residential/foster care. |
| 2 | Is hazardous drinking in a general population survey sample associated with a subsequent increased rate of hospitalization for violence? Is the relationship moderated by sociodemographic factors? | Participants in 2011 Danish National Alcohol and Drug Survey (N=5,126) with complete AUDIT-C responses 8-year follow-up in registers Poisson regression model | Respondents with hazardous consumption (AUDIT-C ≥ 5) had an increased rate of hospital admissions for violence (IRR=2.28, 95% CI=1.16-4.50). Each additional AUDIT-C point associated with 20% increase in incidence rate for violence-related hospitalizations. Significant interaction between gender and AUDIT-C score on hospital admissions for violence. |
| 3 | • Are high AUDIT and AUDIT-C scores associated with increased risk for incident hospital admission for alcohol-related conditions in a general population sample over a seven-year follow-up period? | Participants in 2011 Danish National Alcohol and Drug Survey (N=4,522) who were current or former drinkers, had Danish origin, and had complete AUDIT responses 7-year follow-up in registers Cox proportional hazard model | 56 respondents had a first-time ARDD admission during follow-up. Respondents who scored above AUDIT (score ≥ 8) and AUDIT-C (score ≥ 5) cutoffs had significantly increased risk of being admitted for an ARDD compared to respondents who scored below the cutoffs (AUDIT HR=4.72, 95% CI=2.59–8.60; AUDIT-C HR=7.97, 95% CI=3.66–17.31). |

Note: AUDIT=Alcohol Use Disorders Identification Test; AUDIT-C=Alcohol Use Disorders Identification Test-Consumption; ARDD=Alcohol-related disorders and diseases; HR=hazard ratio; IRR = incidence rate ratio; CI=confidence interval

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| What are the gaps in the literature of register-based studies of alcohol's harms to family members? (Study 1) |
| Is hazardous drinking as measured in a general population survey sample associated with a subsequent increased rate of hospitalization for violence? (Study 2) |
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LIST OF ABBREVIATIONS

| Akaike information criterion |
|--|
| Alcohol-related disorder and disease |
| Alcohol Use Disorders Identification Test |
| Alcohol Use Disorders Identification Test-Consumption |
| Blood alcohol concentration |
| Bayesian information criterion |
| Confidence interval |
| Composite International Diagnostic Interview Substance Abuse Module |
| Diagnostic and Statistical Manual of Mental Disorders |
| European Medicines Agency |
| Hazard ratio |
| International Classification of Diseases, tenth revision |
| International Classification of Primary Care |
| Incidence rate ratio |
| Nordic Medico-Statistical Committee |
| Nordic Medico-Statistical Committee Classification of External Causes of Injuries |
| Preferred Reporting Items for Systematic Reviews and Meta- Analyses Extension for Scoping Reviews |
| Screening, Brief Intervention, and Referral to Treatment |
| World Health Organization |
| |

INTRODUCTION

Compared to other regions of the world, Europe has the highest per capita alcohol consumption and the highest prevalence of binge drinking among adults and adolescents (1). In Denmark, alcohol consumption exceeds the average in Europe (1), and, of the 45 countries and regions participating in the Health Behaviour in School-Aged Children Survey, Denmark has the highest prevalence of past-month drinking and drunkenness among 15-year-olds (2).

High levels of alcohol consumption, and binge drinking in particular, have been causally linked to adverse health consequences, increasing risk of both communicable and noncommunicable diseases (1). Alcohol use is the third leading risk factor for death and disability in Denmark (3). It was estimated that, in 2010, 5% and 9.5% of all deaths among Danish women and men, respectively, were attributable to alcohol (4). The worryingly high levels of drinking among youth prompted the Danish Cancer Society, in partnership with other national and international organizations, to launch a nationwide awareness-raising campaign and advocate for changes in legislation to reduce alcohol availability (5).

Alcohol results in considerable harm to others than the drinker as well. When an expert committee in the United Kingdom was tasked with ranking substances based on harm to the user and others, alcohol was rated number one both in terms of overall harm and in terms of harm to others (6), above heroin and crack cocaine, largely owing to the high prevalence of alcohol consumption. In Denmark, results of a national survey showed that 44% of respondents had experienced either physical or verbal abuse, fear, damaged personal items, or being kept awake at night due to others' drinking in the past year (7), and nearly one in five respondents reported being negatively affected by the heavy drinking of family or friends (8).

The well-established relationship between alcohol and social and health harm to the drinker and others makes alcohol a priority area in the field of public health in terms of research, policy, and prevention (1, 9). While alcohol consumption may be understood and studied from different, but not wholly independent, perspectives in the social sciences (10, 11), the epidemiological public health perspective has been described as taking a problemoriented approach to drinking, with alcohol marked as a risk factor for disease/harm, or as the harm itself (in the case of alcohol dependence, for instance) (12), although potential benefits have also been explored (13). Whether an epidemiological study is assessing, for instance, levels of alcohol consumption in a population, prevalence of drinking patterns, or the relationship between alcohol and health and social outcomes, the underlying aim of such work is to prevent alcohol-related problems (12).

Conducting epidemiological research on alcohol's harms to the drinker and harms to others, however, requires making complicated methodological decisions at a basic research design level. Merely defining what constitutes an alcohol exposure and what constitutes a harm is a complex task. And even when the initial question of how to define the exposure and outcome has been answered, further challenges remain to determine the appropriate data sources to measure these constructs. At the population level, alcohol sales and taxation data are regarded as a crucial source of information on population consumption (14, 15). At the individual level, especially when assessing acute intoxication, alcohol biomarkers, such as blood alcohol concentration (BAC) levels (16), may be used. However, more commonly, subjective measures, and in particular self-reports from population surveys, are used both in studies of alcohol's harms to the drinker and to others (14, 15, 17) to assess exposure and/or outcomes. Another source of information which can contribute to defining and measuring alcohol exposure and harm are registers. Registers consist of individual-level data on a complete target population, which have been systematically collected and regularly updated to reflect changes at the individual level (18).

Although surveys have been the dominant source of information on the relationship between alcohol and harm to the drinker and to others (19), registers have certain features, discussed in detail subsequently in this thesis, which make them apt to address limitations of survey data. In terms of their relationship to each other, it has been noted that register and survey data "are best treated as complementary sources of data" (20) (p. 126).

Within the overall theme of using survey and register data to study alcohol-related harm, this thesis is composed of two distinct parts. Part 1 examines how register data contribute to an understanding of alcohol's harms to family members. This is done by conducting a scoping review to assess and describe existing register-based studies of the relationship between heavy drinking and negative consequences for relatives of the drinker (Study 1). In Part 2, survey and register data are applied to examine harms to the drinker. This part consists of two studies which investigate whether self-reported hazardous drinking in surveys is associated with subsequent hospitalizations for violence (Study 2), as well as alcohol-related disorders and diseases (ARDD) (Study 3), recorded in a patient register. The research

questions of each study are outlined in the next section, and the articles associated with the individual studies are included in the Appendix.

Research questions

Study 1: How do register-based studies contribute to our understanding of alcohol's harms to family members? A scoping review of relevant literature

Despite numerous discussions by researchers concerning the potential contribution of register-based studies on alcohol's harms to others (17, 21, 22), the existing body of research had not been reviewed prior to the present thesis. Scoping reviews are a useful tool for providing an overview of a previously uncharted body of research, especially in cases where the literature is diverse (23). Study 1 mapped the existing register-based literature on alcohol's harms to family members to identify methodological characteristics of studies (research questions 1-3 below) and identify gaps in knowledge (research question 5). As well, the study examined the implications of the methodological features of existing register-based studies for an interpretation of their findings (research question 4). Study 1 contributed to the thesis by providing an overview of the extent to which register-based data have been employed in exploring an important area of alcohol-related harm research and by highlighting the unique contributions of register-based studies, when compared to survey-based studies. The following specific research questions were addressed:

- 1. Which family members, in terms of relationship to the drinker, are the focus of existing register-based studies?
- 2. How has the exposure been operationalized?
- 3. What harms/outcomes for family members of heavy drinkers have been investigated?
- 4. What are the main findings of register-based studies, and how do the findings differ from those of survey-based studies, if at all?
- 5. What are the gaps in existing register-based research on alcohol's harms to family members?

Study 2: Hazardous drinking and violence-related hospitalizations in the Danish general population: A historical cohort study

This study used national registers to track survey respondents' hospitalizations for violence-related injuries over an eight-year follow-up period to investigate the alcohol-violence victimization association. It contributed to the thesis by demonstrating how linking survey and longitudinal register data can be used to assess a relationship that has primarily

been explored through surveys and by case-control and case crossover research. The study addressed the following research questions:

- 1. Is hazardous drinking as measured in a general population survey sample associated with a subsequent increased rate of hospitalization for violence?
- 2. Is the relationship between hazardous drinking and later hospital admission for violence moderated by sociodemographic factors?

Study 3: Using the Alcohol Use Disorders Identification Test to predict admission for alcohol-related conditions in the Danish general population: a record-linkage study

This was a validation study of the AUDIT (Alcohol Use Disorders Identification Test) and the AUDIT-Consumption (AUDIT-C). By using linked survey and register data, this study contributed to the thesis by investigating whether AUDIT and AUDIT-C scores from a survey predicted serious, fully alcohol-attributable outcomes for the drinker, as measured by hospital admissions recorded in a patient register. Although numerous AUDIT and AUDIT-C validation studies have been conducted previously, the cross-source linkage method used in the present study afforded particular advantages when assessing predictive validity, including a long follow-up and an assessment of a broad range of precisely defined alcohol-related conditions.

The research question addressed by the study was as follows: Are AUDIT and AUDIT-C scores associated with risk for incident hospital admission for ARDD in a general population sample over a seven-year follow-up period?

BACKGROUND

This section is an introduction to the main variables used in the present thesis. It first considers the outcome variable of harm from the standpoint of those who are harmed (first or second person) as well as what sorts of harm are incurred. It then examines how alcohol intake is measured and, lastly, reviews the advantages and disadvantages of survey data and register data with respect to the study of alcohol-related harm.

Categorizing harm

Harms to the drinker and harms to others

One general distinction in the area of alcohol-related harm concerns the object of the harm and whether the person experiencing harm is the drinker or another. As a research topic, the adverse effects of alcohol consumption on the drinker remain more examined than harms to others, although activity in the area of alcohol's second-hand harms has increased over the last two decades (24). For instance, at the international level, the World Health Organization (WHO) coordinated a study to quantify and analyse harm to others from drinking in low- and middle-income countries (25). As well, researchers in the Nordic countries working on this subject formed the H2O Nordic research network in 2013 to carry out collaborative qualitative and quantitative studies (e.g., (7, 8)).

The range of harms to the drinker that has been a focus of research is broad and includes health risks, such as risk of communicable diseases, cancers, injuries, and premature mortality (26-29); mental health (30, 31); and socioeconomic consequences (32, 33). Research on the second-hand effects of alcohol use, which within the last decade has coalesced under the research paradigm of "alcohol's harms to others", has also covered a broad range of outcomes at the individual and collective levels that may be related to a single drinking episode or to a pattern of drinking over time (22). On an individual level, outcomes in the area of alcohol's harms to others have been defined to include minor consequences, such as disrupted sleep from noisy partygoers, but also severe outcomes, such as injuries from drink-driving and physical abuse (7, 34, 35). Children of heavy drinkers have been a particular focus of research in terms of academic performance, health outcomes, substance abuse problems, and emotional and mental distress (36-38). On the societal level, studies have investigated costs from drinking, such as treatment for illnesses and absenteeism (39, 40). Further outcomes have included less tangible harms that fall under a category of fears of experiencing harms, such as feeling afraid in or avoiding public places (22, 34). In this thesis,

Study 1 assessed harms to family members of the drinker, while Study 2 and Study 3 examined health-related harms to the drinker.

Alcohol-attributable harms

A further distinction which cuts across both harms to the drinker and to others concerns whether or not a harm is considered fully attributable to alcohol. Fully alcohol-attributable harms are those for which the alcohol-attributable fractions are 100%, meaning that 100% of morbidity and mortality associated with these outcomes would disappear without alcohol (1, 4). In other words, alcohol is required for a person to experience this harm – persons unexposed to alcohol will not have the outcome. That alcohol is a necessary component of these harms is reflected in the nomenclature, with the word "alcohol" featured in the name of the condition (e.g., alcohol use disorders and alcoholic hepatitis) (41). The terminology of fully alcohol attributable has largely been reserved for medical diagnoses (with the crime of drink-driving being an exception (12)). However, whether a disorder or disease is diagnosed as alcohol-related is likely also influenced by social factors (42), as for instance, such diagnoses may be underused due to the stigma attached to alcohol-related conditions (43, 44).

Aside from fetal alcohol syndrome, health-related harms designated as fully alcoholattributable overwhelmingly concern the drinker. In this thesis, Study 3 investigated whether AUDIT and AUDIT-C scores from a general population survey predict hospital admissions for fully alcohol-attributable conditions (see Table 4) recorded in a medical register (45).

The vast majority of alcohol-related harms, however, are not categorized as fullyattributable to alcohol. In their classification of alcohol-attributable harm, Rehm and colleagues (13) use the term partially-attributable to alcohol to refer to harms that have been assessed as having a causal association with alcohol but may also occur in the absence of alcohol (4, 13). This means that there are other pathways to the harm that do not involve alcohol – some individuals not exposed to alcohol will experience the harm. Conceptualized under the sufficient cause model (13, 46, 47), alcohol is one component, which, in concert with other components, form the sufficient conditions for an outcome to occur.

Intentional injuries, the overarching category under which physical violence victimization (Study 2) falls, has been assessed by some researchers as being partially-attributable to alcohol (1, 13). The association between alcohol consumption and risk of intentional injuries for the drinker has been previously demonstrated by studies using largely case-control and case-crossover methodologies (29, 48-50) but also by survey-based longitudinal studies

(e.g.,51). In some prior studies of alcohol and violence, data were hospital-based in the sense that the study samples were drawn from emergency departments (48, 52) or from hospital registers (53). In a review of international emergency room studies, for instance, Cherpitel (48) concluded that such studies show that emergency department patients with violence-related injuries are more likely to have positive BAC results or report that they had been drinking than patients suffering from other types of injuries. As well, an analysis using Swedish register data showed that, compared to the general population, individuals with substance use disorders have a nine-fold higher risk of being a homicide victim (54). Study 2 builds on the existing body of research on alcohol and violence by using a methodology which links general population survey data on drinking with longitudinal hospital register data on violence victimization.

As regards harms to others (Study 1), road traffic injuries caused by others' driving have been assessed as partially-attributable to alcohol and are included in burden of disease estimates, but other injuries (e.g., interpersonal violence) and other harms to others (aside from fetal alcohol syndrome) are not currently accounted for (1). As is the case for harms to the drinker, with a few exceptions (e.g., criminality described in (55)), the "alcoholattributable" terminology has been associated with disease and medical harms to others, as opposed to social harms. However, some social harms to others could also be considered to be wholly alcohol-attributable. For example, "spending household money on alcohol" or vehicle impoundment of the family car due to a drink-driving arrest may be candidates for fully alcohol-attributable harms, as they would not occur without the presence of alcohol.

Categorizing alcohol exposure

In research on alcohol-related harms, alcohol exposure can be categorized roughly in terms of abstention status within a defined period (e.g., drinker vs. non-drinker) but is frequently operationalized in ways that allow for more detailed categorizations, such as by average volume of consumption in terms of frequency of drinking and amount of alcohol consumed, or patterns of drinking, often as frequency of heavy episodic drinking (14, 15, 56-59). Further considerations include the time accounted for by these variables, for instance past year, past three months, or most recent drinking occasion(s) (14). Additionally, exposure can be defined by meeting criteria for an alcohol use disorder diagnosis or by scores on a screening tool (59), such as the Michigan Alcoholism Screening Test (60) or CAGE (61),

which screen for severe alcohol disorders (62), or the previously-mentioned AUDIT, which assesses both alcohol consumption and alcohol problems (63).

The AUDIT is a 10-question self-report screening tool designed to identify hazardous and harmful alcohol use, including possible alcohol dependence (63). The tool was developed at the request of the WHO approximately 30 years ago by a team of international researchers with the main aim of creating a simple means of detecting excessive drinking among patients in primary care settings (63, 64). The AUDIT is promoted by WHO as a tool for identifying individuals who may benefit from a brief alcohol intervention to reduce hazardous and harmful alcohol consumption (63, 65). In its design, the AUDIT "conceptual domain" of "hazardous alcohol use" was considered to be covered by items 1-3; "dependence symptoms" by items 4-6; and "harmful alcohol use" by items 7-10 (63) (see the Methods section of this thesis).

Although the AUDIT's brevity and simplicity are counted among its advantages (63), the 10-item tool may still be too burdensome to be incorporated in practice in certain settings, such as general practice or emergency departments (66, 67). The AUDIT-C, which consists of the first three items of the full AUDIT, was developed to address such issues of feasibility and reflects the importance of frequency of heavy drinking episodes for identifying alcohol problems (66). The AUDIT was initially intended for healthcare settings, but in the years since its development, its reach and application have expanded broadly to other settings. The AUDIT and AUDIT-C are now frequently incorporated in research studies (68, 69) and in general population surveys of drinking behaviors (58), such as the 2011 Danish National Alcohol and Drug Survey. Based on the data from this 2011 survey, the AUDIT and AUDIT-C were used as measures of exposure in Study 2 and Study 3 of this thesis.

The AUDIT and AUDIT-C have been the focus of numerous previous validation studies, which have, for instance, tested how the tools performed in different countries (70-73), with different subgroups (74, 75), and among general population samples (76). AUDIT validation studies have also frequently examined the tool's factor structure (77-80). Studies of the psychometric properties of the AUDIT administered in various populations have yielded differing findings regarding the factor structure of the AUDIT, with some studies supporting the original three-factor structure outlined by the AUDIT developers (73, 81), while other studies have found that two-factor (e.g., alcohol consumption and drinking problems) (77, 78, 82) or a single-factor solution (79, 83) provided the best fit.

Other AUDIT and AUDIT-C validation studies have explored test-retest reliability (84-86), or have compared the AUDIT's and AUDIT-C's performance against diagnostic interviews (e.g., the Composite International Diagnostic Interview) for detecting current alcohol use disorders (87, 88).

To summarize, alcohol exposure can be, and has been, defined and measured in a multitude of ways in research. This issue is further explored in Study 1 through an investigation of how alcohol exposure has been operationalized in register-based research of alcohol's harms to family members.

What are the main data sources of alcohol exposure and alcohol-related harm?

A related concept to categorizing study variables, such as alcohol exposure and harm, is determining the appropriate data sources to measure these variables. In the remainder of the introduction, further background will be provided on how surveys and registers have been used to measure alcohol exposure and outcomes, and the methodological considerations of each approach will be explored.

Use of survey data

Survey research involves collecting data from a representative sample of a well-defined population through the use of a questionnaire (89) and may also include structured interviews (90). Such surveys are a key measurement tool for both alcohol-related exposure and outcome variables in studies of harm to the drinker and to others (17, 58, 91, 92). In a recent commentary, Rehm et al. (19) described surveys as the "backbone of alcohol epidemiology" (p. 162).

In terms of exposure, survey questions can be used to provide a broad distinction between exposed and unexposed, for instance asking if a respondent has consumed any alcohol in the past 12 months, or if they had ever engaged in binge drinking (93). Often, particularly in general population alcohol surveys, questionnaires include items that allow for more detailed categorization of exposure in terms of the respondent's consumption, notably in the form of a general or beverage-specific quantity-frequency measures (14, 15, 56-59, 94), which allow for the calculation of mean volume of consumption. These questions address how often the respondent drinks (e.g., "In the past year, how often did you drink any alcoholic beverage?") and how much (e.g., "How many drinks did you usually have on days you drank in the past year?") (94). As well, questions to assess frequency of heavy episodic drinking are typically

included in questionnaires (14, 15, 56, 57, 94) (e.g., "How often in the past 12 months, have you had six drinks or more on one occasion?"). In surveys used to assess harms to others, respondents may be asked whether they lived with a person with an alcohol problem during their childhood (95) or if they were ever married to a person with an alcohol problem (96).

There are wide variations in the way in which frequency, quantity, and pattern of drinking questions are implemented (59, 97), and in an attempt to ensure comparability and application of best practice, there have been numerous efforts to develop guidelines for measuring alcohol consumption in surveys (94, 98-100). However, these may not be employed consistently in practice (94).

Standardization may also be achieved through the incorporation of established screening and diagnostic tools into surveys, such as the Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM) (101) and the above-mentioned AUDIT (63). Such screening and interview tools can be used to identify respondents with problematic drinking (i.e., the exposure). For instance, the interview tool CIDI-SAM was designed to enable crosscultural comparisons of epidemiological studies and to be used by non-clinicians to identify survey respondents who meet the criteria for alcohol use disorders, consistent with, for instance, the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD-10) (58, 101, 102). Both the AUDIT and the CIDI-SAM include questions on drinking frequency and quantity, pattern of drinking, and negative consequences from drinking. The AUDIT (previously discussed in the section "Categorizing alcohol exposure") was included in Study 2 and Study 3 this thesis, and will be described in more detail in the Methods section.

Surveys are also often used to measure outcomes in studies investigating alcohol-related harm. However, one feature of epidemiological alcohol research, which is infrequently found in survey research on other risk factors, is the inclusion of questions on predefined risk-factor-related consequences (58, 103, 104). That is, survey questions are often worded such that the causal association with alcohol is already made. For instance, in surveys of harms to the drinker, a respondent might be asked if they had ever "lost a job, or nearly lost one, because of drinking" (105) or if there was "ever a time that you felt your alcohol use had a harmful effect on your physical health" (106). In surveys addressing alcohol's harms to others, respondents might be asked, in reference to the drinker, "Were you emotionally hurt or neglected because of their drinking?" (107). The issue of individual survey questions

linking exposure and outcome is discussed further in the subsequent section on the strengths and limitations of survey-based research.

Methodological considerations of survey-based research

Surveys have many features which make them apt for use in alcohol research. Surveys are efficient ways of gathering information on large groups of people, and, in the case of general population surveys, provide data on a representative sample of the national population (108). A particular advantage is that surveys can capture a high level of detail on level and pattern of drinking, including abstention status and heavy episodic drinking, which are unavailable when other sources, such as sales or taxation data, are used. As well, as opposed to register data sets, survey-based measures are not based on a service contact, such as a treatment episode, hospital admission, or an arrest - events which usually reflect the severe end of the spectrum in terms of alcohol exposure. Thus, surveys are able to capture non-clinical populations and exposure levels that are more commonly found in the general population. Questionnaires are also used to collect detailed data on important non-alcohol-related variables, such as other behavioral factors, socio-economic factors, age, and gender, which can be used to control for confounding in the analyses and permit subgroup analyses. Alcohol surveys also enable comparisons among participants in regard to scores on established tools, such as the AUDIT (108). Lastly, surveys are able to measure outcomes that are not easily assessed by other sources. For instance, subjective outcomes, such as "being emotionally hurt", fears (e.g., "Has it ever happened that you have been afraid of drunken people on the street or in some other public place?" (7)), and fears of harms ("fears about going to places" where heavy drinkers will be present" (109)) can only be measured by self-reports.

However, there are several important limitations associated with alcohol-related survey studies. Notably, surveys severely underestimate population consumption, accounting for only 40-60% of alcohol consumed compared to sales data (110) and also underestimate the prevalence of heavy drinking and harmful alcohol use (111) in the general population. This underestimation is thought to stem from several sources, which fall under the general categories of selection bias and information bias, and are of concern also in individual-level alcohol research studies.

As regards selection factors, one concern is that groups that are more likely to have particular drinking patterns or to be heavy alcohol users, are filtered out or missed both at the sampling stage and at the response stage of survey studies (15, 19, 112). For instance, in

terms of sampling, if the survey study sample is drawn from private households or telephone directories, certain groups, such as university students living in on-campus housing, those who are incarcerated, and those who are homeless, will be excluded or under-sampled (15, 19, 112, 113). In terms of response, there is evidence that survey non-respondents differ systematically from respondents in their sociodemographic features (112), but, also, notably, in their own heavy and hazardous drinking and abstention status (114-116) and their family members' level of alcohol problems (117). Reduced participation among heavy drinkers and people with alcohol problems also affects survey research on alcohol's harms to others (118), as many of the findings on this topic are based on the reports of respondents (in the role of the drinker) inflicting harm on others. Concerns about the representativeness of survey studies are particularly in focus of late, given that survey response rates in general have been declining markedly (119).

Regarding the potential for information bias, there is evidence that self-reports of alcohol consumption are inaccurate, with a tendency toward underreporting (15, 110, 120). Some studies also show that this underreporting might differentially affect certain groups of drinkers, with sporadic and hazardous drinkers more affected (121, 122).

As mentioned previously, in survey-based alcohol research, the exposure and outcome are often presented in a single question such that the question presupposes that the outcome is attributed to alcohol. For instance, respondents are frequently queried as to whether they have experienced an outcome "due to alcohol" or "because of" their own, or another person's, drinking (e.g., "Were you physically hurt because of their drinking?"(107)), with the causal attribution in the question being very explicit. Or the attribution may be made by linking the alcohol and the outcome proximally in time (22) (e.g., "Did you ever get into physical fights while drinking or right after drinking" (92). Bloomfield et al. (58) summarize the perception that this is a unique feature of alcohol research by remarking that "only in alcohol epidemiology, the measurement of the risk factor (alcohol) is already implicitly associated with the outcome" (p. 352). According to Gmel and co-authors (103, 104), this type of question violates the epidemiological standard of measuring exposure and outcome independently and is problematic for several reasons. For instance, such questions require subjective assessments, which are unreliable and vary based on individual, cultural and temporal characteristics and therefore should not be used as a basis for establishing a relationship between alcohol and outcomes (22, 103). In addition, such questions predetermine the causal direction such that alcohol use is specified as the antecedent variable

that leads to a particular outcome, such as financial troubles, rather than vice versa (103, 104).

Similar critiques of survey-based research specifically on alcohol's harms to others have been made regarding questions that require the respondent to make an attribution that an experienced harm was due to alcohol (17, 22). However, a further complication of harms to others survey research is that such questions may require the respondent to make an assessment that another person had been drinking or was intoxicated at the time of an alleged harm. Respondents may not have sufficient information to make these assessments, particularly in regard to assessments of strangers' behaviors (17) (e.g., "Has it ever happened that you have been kept awake at night by noise from drunken people in the neighborhood or in the street?" (7)). In a review of survey-based studies of alcohol's harms to others, Rossow (17) also noted that, frequently, survey questions addressing some outcomes, such as "family problems" and "neglect", are problematically vague in the sense that they lack sufficient detail to characterize the specific harm inflicted, its severity, or its duration.

However, despite concerns associated with survey questions that contain predetermined alcohol attributions, there are good reasons to preserve their inclusion in questionnaires and to study such items. Gmel et al. (104) notes that while such questions should not be used to assess the relationship between alcohol exposure and outcomes, they do have value in alcohol research as a component of standardized screening tools embedded in surveys and used to assess alcohol use disorders and hazardous and harmful drinking, such as the AUDIT. As well, for some harms to others, the built-in attribution may be the crux of the harm, as, for instance, a respondent reporting that their spouse's drinking causes problems is evidence of marital problems due to alcohol (42).

A further limitation of survey research is that, given time and space constraints, the spectrum of harm to be reported is by nature rather narrow on survey questionnaires or interviews, as the number of questions to be asked of each informant is limited. Rare and extreme outcomes will only be relevant to a small number of respondents. Thus, surveys tend to focus on the most commonly experienced outcomes, and as a result, more severe forms of harm are less explored (17, 20).

It has been proposed by some alcohol researchers that many of the shortcomings of population surveys could be addressed by complementing such research with register-based

data (17, 118). An overview of register-based research and the strengths and limitations of this methodology will be covered in the next sections.

Use of register data

The United Nations Economic Commission for Europe defines a register as "as a systematic collection of unit-level data organized in such a way that updating is possible...a register will contain information on a complete group of units, a target population (e.g. persons, buildings, firms). These units are defined by a precise set of rules (for instance resident population in a country), and the attributes are updated in line with changes undergone by the units" (18) (p. 15). Most registers were originally developed for purposes that could be categorized as administrative (123), as opposed to statistical or research, including for "registration, transaction and record keeping, usually during the delivery of a service" (124) (p. 84). However, medical databases or clinical quality databases, such as the Danish Lung Cancer Register, National Diabetes Register, and the Danish Stroke Registry, have been developed to monitor specific diseases and treatments with the unique aims of surveillance, quality control in terms of diagnoses and treatment, and patient safety (125, 126).

Although not primarily developed for research purposes, registers can serve multiple functions in research. In their guidelines on register-based studies, the European Medicines Agency (EMA) defines this methodology as an "investigation of a research question using the data collection infrastructure or patient population of one or several patient registries" (127) (p. 4). The EMA notes that in some countries, a subset of register-based studies use "datasets created by a comprehensive registration of administrative and healthcare data of the population at the regional or national level" (p. 5) This is particularly true in the Nordic countries, which have a long history of collecting data on regional and national residents and, in recent decades, organizing such information in electronic registers (128). Although the EMA guidelines focus on medical research and, thus, refer to "patient populations" and "patient registries", the range of available registers, especially in the Nordic countries, is extremely broad, and, in addition to healthcare contacts, specific disease diagnoses, prescriptions, biobanks, and mortality, also cover non-medical areas such as labor market participation, academic performance and criminality, among many others (129). Thus, registers are apt for capturing a wide range of potential exposures and outcomes in research. Register-based studies can solely use register data or can use register data to supplement

other datasets, such as surveys or genetic data. Registers can also be used to generate representative samples for research (128) and to study and adjust for survey non-response (117, 130).

Although the Danish Government has been maintaining registers for nearly 150 years (e.g., since 1875, for causes of death register (131)), the full research potential of register data was not realized until the establishment of the Danish Civil Registration System and the associated personal identification number (Det Centrale Personregister number) in the 1960s (129, 132-134). This unique number made it possible for different registers to be linked directly and, crucially for longitudinal studies, for individuals to be tracked over time until death, emigration, or event of interest (129, 132-134). In countries where unique identifiers are not available in all registers, an alternative is to use probabilistic matching (134, 135), as has been applied in Australia, for instance (136). In terms of health-related research, such as studies that use hospital register data, another crucial feature of the Danish and other Nordic systems is the government-funded universal health coverage, which ensures that such registers have near complete coverage (132). This contrasts with some administrative medical data that are available in other countries, such as from private insurance providers like Kaiser Permanente in the United States, or for certain employment categories, such as veterans (132, 137, 138). In these cases, coverage is limited and subject to selection bias, and in the case of private insurance providers, the population is open, and members enter and exit frequently, resulting in medical histories and follow-ups that are substantially incomplete.

Register-based research is a broad category, and, within the field of alcohol research, covers many different applications of register data. As mentioned previously, studies may be exclusively register-based, meaning that the study population is drawn from a register and all measures are taken from registers. For instance, in their investigation of the association between alcohol use disorders and suicide, Edwards et al. (139) drew their cohort from the Swedish population register (i.e., Swedish citizens born between 1950 and 1970) and used register data for the predictor and outcome variables, as well as covariates. In this study, the primary predictor – an alcohol use disorder diagnosis – was identified using medical, criminal and prescription registers, and the outcome – suicide – was identified using the mortality register. As well, confounding due to other psychiatric disorders and familial factors was investigated using the previously mentioned registers, as well as the Multi-Generation Register, which was used to identify cousins, half siblings, and full siblings of the study population.

Another version of register-based research involves the linking of register data with other datasets, such as surveys. As noted by Schmidt et al. (140), the abundant register data in Denmark has the potential, in effect, to turn every survey study into a cohort study with long-term follow-up.

Methodological considerations of register-based research

General population alcohol surveys frequently have study populations of several thousand participants; however, register-based research has the potential to include even larger samples - for instance, in theory, all residents of Denmark could be included in a given register-based study. Such large sample sizes provide a statistical advantage over other study designs, as the analyses have sufficient power to detect hypothesized effects (134, 141). Since participants do not opt in or out of register-based studies (see the section on Ethics), register-based samples do not suffer from issues of non-response or from significant loss to follow. Therefore, the samples can be viewed as representative, and biases attributable to selection and attrition are minimized (134). Register data are often available over extended periods, frequently covering a participant's entire lifetime, enabling examination of long-term consequences and outcomes with long induction or latent periods (130). As well, because the data are collected prospectively, register-based studies may be better able to assess causality compared to survey-based studies, which are generally cross-sectional. Further, the wide coverage and long follow-up time mean that registers are apt for capturing rare but severe outcomes (17, 134) and for targeting narrowly defined or hard-to-reach subgroups (118, 134, 142). While tracking participants over long periods is also possible in survey-based cohort studies, such studies are very expensive, necessitate long waiting periods, and are logistically more complicated, not to mention the high risk of attrition.

For certain indicators, such as income, education level, employment status, and medical diagnosis, which are relevant exposure, outcome, mediating, and confounding variables in alcohol research, register data can provide very detailed and accurate information (130). Another relevant advantage is the ability of registers in the Nordic countries to easily identify relatives through unique family and spouse identification numbers and population registers and to link registers in order to assess outcomes for family members. In the area of alcohol research, this permits assessment alcohol's harms to family members (e.g., children and spouses) but also of the contribution of genetic factors, for instance via twin studies or by examining lived-with versus not-lived-with parents (118, 130).

A considerable practical advantage of register-based studies it that they make use of existing data. Although there are financial expenses and lag times associated with obtaining register data (118), these are generally minimal when compared with the costs and time associated with obtaining similar information through primary data collection, such as in survey-based cohort studies (143). The use of existing data also reduces the burden on research participants, which may be a significant advantage given that survey response and follow-up rates are declining (119).

Furthermore, since register data are not collected primarily for research purposes, and therefore exposure information is collected independently of outcome status, the risk of recall bias is reduced, compared to, for example, a survey-based case-control study in which the cases and controls might have differential recall of exposure information (130, 134, 143). Although this level of independence from the research question is associated with certain advantages, it can also be considered a limitation. That is, as the variables are not defined or recorded by the researchers conducting the study, the available information may not precisely match the study's aims (128). The categories in the registers may be too broad or certain information on relevant confounding variables may be altogether absent from the register (134). For example, registers do not contain detailed information, or any information at all, on smoking behaviors, diet, or use of over-the-counter medications.

The above-mentioned issues regarding indicators that are absent or not sufficiently detailed means that proxy variables are often used in register-based studies to measure exposures, outcomes, and confounding variables (130). For instance, prescription fills recorded in registers are used as proxies for medication ingestion/treatment or as a proxy for disease occurrence (e.g., purchase of prescription medicines for alcohol abuse/dependence are used as a proxy for the presence of an alcohol use disorder (144)) or for access to and use of health services (145). Mäkelä et al. (20) argue that, as such, certain register data are not direct measures of variables but, rather, are measures of "service use". Thus, although register-based studies are not affected by non-response bias, as survey-based studies are, register-based data suffer from a different form of selection bias in the sense that these data only reflect those individuals who are in contact with particular institutions, such as the hospital or substance use treatment system. This is more or less of a concern depending on the particular research question. For instance, as mentioned by Miettunen et al. (128) in their discussion of the use of register data in psychiatric epidemiological research, for some conditions, such as chronic psychotic disorders, hospital registers will generally include most

cases since the majority of people with this condition will eventually receive hospital-based treatment. However, people with other conditions, such as personality disorders or depression, may never receive hospital (or any) treatment, and, thus, hospital register data may fail to capture a large proportion of individuals with these conditions (128). Thus, rather than serving as a random sample of individuals with a condition, the "service users" included in such studies may not be representative (20). Relatedly, an oft-mentioned limitation of register-based data concerns the "tip of the iceberg" issue (128, 146-149), referring to the fact that registers only capture individuals whose problems are severe enough to put them in contact with, for example, the hospital or criminal justice system, and will therefore, in the case of alcohol research, miss a substantial portion of individuals with less severe, or newly developed, problematic drinking. As regards alcohol-related variables, then, register sources may be more apt to assess alcohol use disorders but not subclinical forms of heavy drinking.

Apart from factors related to the severity and duration of problems, there may be other reasons why individuals do not appear in registers (20). In their comparison of register- and survey-based data sources on alcohol problems, Mäkelä et al. (20) reported that individuals found in healthcare registers were less likely to be female, highly educated, employed, and of younger or older ages. Since the analyses controlled for both the self-reporting of consumption and the self-reporting of service use (via responses to the Regional Health and Wellbeing Study, such as AUDIT-C scores and answers to the question "Have you used the following services for substance-abuse-related problems during the last 12 months?"), the authors suggest that these findings may be due to some processes related to the recording of service use. They proposed explanations related to "acknowledgement of problems in individuals representing groups where the problems are less frequent" or "avoidance of stigmatisation" (20) (p. 138). As previously discussed, social desirability bias is a concern in survey studies, since, due to the stigma associated with alcohol problems and heavy drinking, participants may not accurately report alcohol consumption and harms. However, stigmatization also affects register-based data. Alcohol-related disorders are particularly stigmatized conditions (150) and therefore may be underreported in administrative data, for example, as a cause of death (43, 44).

Since register data collection is usually not controlled by the researchers, there may be uncertainty about the quality of the data in terms of its usefulness for research purposes. For instance, with respect to diagnoses, there may be variation in coding between medical secretaries or between hospitals, which could affect data quality (134). As well, motivations

related to reimbursement may influence coding practices such that some diagnoses and treatments are more likely to be used (i.e., diagnostic drift) (134, 151). Validity studies (e.g., 152, 153) have been carried out for some registers and for particular health-related conditions recorded in registers, which give some indication of the accuracy and completeness of the register and therefore its value as a data source for research (142). Errors in medical registers may be considered diagnostic or administrative, with the former referring to errors made by the clinician in diagnosing the patient (e.g., by missing certain symptoms) and the latter referring to errors that occur when the diagnostic information is coded and entered into the register (154). In many validity studies used to assess register accuracy, medical records or research interviews are used as the "gold standard", and validity and completeness can be evaluated by calculating the positive predictive value (# of true cases in register/total cases recorded in register) and the sensitivity (# of true cases in register/total number of true cases) (134, 142), respectively. In the area of alcohol-related conditions, several relevant validity studies have been carried out. One early study of Finnish hospital discharge data found high agreement between the medical record and the discharge register for five alcohol-related primary diagnoses (155). In a validity study of psychiatric diagnoses recorded in the Norwegian psychiatric hospital register, researchers found "fair" agreement between substance use disorder diagnoses recorded in the hospital register and diagnoses given following a structured diagnostic interview and review of medical records (156). However, despite some validity research, the existing studies are limited both in the registers included (i.e., primarily focused on psychiatric hospital registers) and the diagnoses assessed, and further studies are warranted to show the validity of other registers and the full range of alcohol-related conditions for research purposes.

Although, in the Nordic countries, the coverage of registers is very good (e.g., nearly all individuals who visit a hospital in Denmark will be recorded in the hospital discharge register), there are still issues of missing data. In register data (e.g., in the case of hospital admissions), an absence of an entry is often treated as non-occurrence of an outcome or exposure. However, there are cases of true missing data. For instance, medical and educational histories may be incomplete for immigrants and other residents who have spent long periods abroad (134). Or, for reasons discussed previously, a lack of a diagnosis in a register may not equate to an individual being disease-free, since, for many conditions, an individual may have a disease or disorder without having any medical contacts related to that condition and thus simply go unregistered. Or, for some conditions with long latent periods,

the initial register entry might not represent onset. So, there can be uncertainty about what "missing" means in the context of register-based data (134).

Another concern with the use of register data, is the issue of left censoring or left truncation (132-134, 157). This refers to the fact that there is no information available to researchers prior to the establishment of the registers. This can lead to misclassification of exposures and outcomes, as any instances of exposure and outcomes that occurred before the start date of the register will not be accessible to researchers. This is also a relevant issue for survival analysis and studies looking at incident cases, for example.

Lastly, a previously-mentioned strength of register data, namely, the potential to generate large sample sizes, can also be considered, if not a limitation, a reason for reflection. Thygesen and Ersbøll (134) point out that there may be a concern that some register studies may be overpowered, meaning that the very large sample sizes could generate findings that are statistically significant, but, upon reflection, may not be clinically important (134). In such cases, findings should be interpreted alongside other indicators, such as effect sizes, and additional measures, including alcohol-attributable fractions, that can be used to convert statistical relationships into meaningful figures for decision makers. Thus, there is a need for consideration of the nature of the variables under study, including the prevalence of the exposure and severity of the outcome, in order to assess the clinical significance of the findings.

This introductory material has provided an overview of the structure of the present thesis and given background on the exposures, outcomes, and sources used in the research. It has reviewed how the research is composed of two parts. The first part contains a study that reviews the state of the use of register data in studying alcohol's harm to the family. The second part contains two studies that examine the relationship between individuals' alcohol intake, as assessed in a cross-sectional survey at a particular point in time, on the one hand, and harm, as determined in national medical registers over a follow-up period, on the other.

METHODS

Study 1

Study 1 used a scoping review methodology to map the research literature on registerbased studies of alcohol's harms to family members and to identify areas for future research. The review was conducted using the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist (158). While the scoping review methodology shares some features with the more well-known systematic review methodology, there are important differences. Both scoping reviews and systematic reviews are methods used to summarize prior research on a topic. However, the scoping review methodology is distinguished by its objectives of charting all the available literature on a research topic and identifying understudied areas (159, 160). Systematic reviews, in contrast, tend to be more narrowly focused and aim to summarize results of comparable studies on a highly specific topic, often with the further aim of having a practical application, such as to guide healthcare or policy decisions (161). For Study 1, the scoping review methodology was selected, as it is most appropriate to give an overview of the literature and identify areas where research is lacking.

Information sources and search strategy

Studies were identified by searching three electronic academic literature databases (PubMed/MEDLINE, EMBASE and PsycINFO) in August 2019, using subject headings and terms related to the following three categories: relationship to the drinker, exposure, and data source (see Box 1). Additionally, the reference lists of all included records were searched.

The following criteria were employed to select articles for the final review:

- a) Heavy drinking as an exposure; the combination of heavy drinking and illicit drug use into a category of "substance use" was permitted.
- b) Outcome was harm to a family member (immediate or extended) of the drinker.
- c) A register used as the data source for the outcome.
- d) An individual study (i.e., no reviews).
- e) Peer-reviewed and published in English; no restriction on publication date.
- f) Study excluded if only assessed prenatal exposure, perinatal outcomes, or substance-related outcomes.

From the database searches, 5,134 records were identified, and 2,737 further records were identified from reference lists. Duplicates were removed using EndNote X8.2, leaving a total of 5,961 unique records. After the titles and abstracts of all unique records were screened, 403 records were selected for a review of the full text. Following the full-text review, 91 studies were determined to meet the inclusion criteria. The selection process is outlined in Figure 1.

Data charting and extraction

An overview of the included studies was obtained by extracting the following elements from each record and entering the information into a data table: author(s), year of publication, title of article, study focus (i.e., is the family member's substance use a primary focus, among multiple risk factors, or only included as a covariate in the analysis?), study population (including sample size and any special characteristics), length of follow-up, exposure measure (including data source and definition of heavy drinking), relationship between the drinker and family member, outcome measure(s) (including data source and definition), and main findings. This information was then sorted in broad categories and the number of studies in each category was reported in descriptive tables. Some studies included multiple exposure sources and/or multiple outcome measures.

The findings of the subset of studies in which substance use of a family member was the primary explanatory variable (rather than one of various risk factors examined) were summarized using a vote-counting procedure. This method consists in totaling the number of studies with significant positive, significant negative, and non-significant findings (162). A brief narrative summary accompanied the numerical summary.

Box 1. Search strategies for scoping review

| PubMed |
|---|
| (((((((Registries[MeSH Terms]) OR Records as Topic[MeSH Terms]) OR |
| Register*[Title/Abstract]) OR Registry[Title/Abstract]) OR Registries[Title/Abstract]) OR Record |
| linkage[Title/Abstract])) AND (((((((Alcohol*[Title/Abstract]) OR Alcohol Drinking[MeSH Terms]) |
| OR Alcohol-Related Disorders[MeSH Terms]) OR Substance use[Title/Abstract]) OR Substance |
| abuse[Title/Abstract]) OR Drinking Behavior[MeSH Terms]) OR Drink*[Title/Abstract])) AND |
| ((((((((Family[MeSH Terms]) OR Mother*[Title/Abstract]) OR Father*[Title/Abstract]) OR |
| Caregiver*[Title/Abstract]) OR Parent*[Title/Abstract]) OR Maternal*[Title/Abstract]) OR |
| Paternal*[Title/Abstract]) OR Child*[Title/Abstract]) OR Spous*[Title/Abstract]) OR |
| Partner*[Title/Abstract]) OR Sibling*[Title/Abstract]) OR Famil*[Title/Abstract]) AND |
| English[lang] |
| Embase |
| ('register'/exp OR register*:ab,ti OR registry:ab,ti OR registries:ab,ti OR 'record linkage':ab,ti) |
| AND ('drinking behavior'/exp OR 'alcohol consumption'/exp OR 'alcoholism'/exp OR |
| alcohol*:ab,ti OR drink*:ab,ti OR 'substance use*':ab,ti OR 'substance abuse*':ab,ti) AND |
| ('family'/exp OR mother*:ab,ti OR father*:ab,ti OR caregiver*:ab,ti OR parent*:ab,ti OR |
| maternal*:ab,ti OR paternal*:ab,ti OR child*:ab,ti OR spous*:ab,ti OR partner*:ab,ti OR |
| sibling*:ab,ti OR famil*:ab,ti) AND ([article]/lim OR [article in press]/lim) AND [english]/lim |
| PsycInfo |
| (MAINSUBJECT.EXACT.EXPLODE("Family") OR ti,ab(mother*) OR ti,ab(father*) OR |
| ti,ab(caregiver*) OR ti,ab(parent*) OR ti,ab(maternal*) OR ti,ab(paternal*) OR ti,ab(child*) OR |
| ti,ab(spous*) OR ti,ab(partner*) OR ti,ab(sibling*) OR ti,ab(famil*)) AND |
| (MAINSUBJECT.EXACT.EXPLODE("Drinking Behavior") OR |
| MAINSUBJECT.EXACT.EXPLODE("Substance Use Disorder") OR ti,ab(alcohol*) OR |
| ti,ab(substance use*) OR ti,ab(substance abuse*) OR ti,ab(drink*)) AND (ti,ab(register*) OR |
| ti,ab(registry) OR ti,ab(registries) OR ti,ab(record linkage)) |
| |



Figure 1. Flow diagram of records screened, assessed, and included in the scoping review

Note: Some articles were excluded for multiple reasons; adapted from Brummer et al. (163)

Studies 2 and 3

Study 2 and Study 3 were historical cohort studies, in which the study populations were drawn from 2011 Danish National Alcohol and Drug Survey respondents (164). Historical (also known as retrospective) cohort studies can be defined by the fact that, at the time the study is designed (2019/2020, in the case of the thesis), "both the exposures and outcomes have already occurred" (p. 217) (47). Historical data, such as previous surveys and records, are used to assemble the cohort and identify exposures and outcome events.

Both Study 2 and Study 3 used the 2011 survey data (via the AUDIT/AUDIT-C) to define and measure alcohol exposure. Using linked national register data, the cohort was followed in the registers from 1 September 2010 until 31 December 2018 in Study 2, and from 1 September 2011 until 31 December 2018 in Study 3. The details of the studies' methodologies are described in Table 1 and in the text below.

| Component | Study 2 | Study 3 |
|------------------------------|---|---|
| Study type | Historical cohort | Historical cohort |
| Main statistical analysis | Poisson regression | Cox proportional hazards regression |
| Population | Participants in the 2011 Danish National Alcohol and Drug Survey with complete AUDIT- C | Participants in the 2011 Danish National Alcohol and Drug Survey, who were current or former drinkers of Danish origin, with complete AUDIT, and with no history of alcohol-related hospitalization |
| Sample size | 5,126 | 4,522 |
| Follow-up period | 2010–2018 | 2011–2018 |
| Exposure variable and source | AUDIT-C scores from 2011 survey | AUDIT and AUDIT-C scores from 2011 survey |
| Outcome variable and source | Number of hospital admissions with reason for contact specified as violence in National Patient Register | Incident hospital admission with alcohol- related ICD-10 diagnosis from National Patient Register |
| Covariates | Gender, ethnicity, highest level of education, age, prior psychiatric disorders, past-year illicit drug use, cohabitation status, and presence of minor children in the home | Gender, highest level of education, age, prior psychiatric disorders |

| Table 1. Overview of methods of cohort studie |
|---|
|---|

AUDIT: Alcohol Use Disorders Identification Test; AUDIT-C: Alcohol Use Disorders Identification Test Consumption; ICD-10: International Classification of Diseases, tenth revision

Population

The cohort for Study 2 and Study 3 consisted of respondents to the cross-sectional 2011 Danish National Alcohol and Drug Survey (164). The survey was administered via a telephone interview (32%) or Web questionnaire (68%) in September and October 2011 and was conducted by Statistics Denmark on behalf of the Centre for Alcohol and Drug Research, Aarhus University, Denmark (108). The survey included questions related to background and socio-demographics, such as the respondent's gender, age, family, and living situation. The section on alcohol covered age at drinking initiation, frequency and quantity of general and beverage-specific alcohol consumption, and consequences of drinking during the past 12 months. As well, participants were asked about their reasons for drinking or not drinking alcohol and were asked to recall specifics (e.g., location, time, and setting) of their last drinking episode. To reduce the burden on participants, half of the participants received an additional section covering their opinions on drug and alcohol policy and attitudes toward drug and alcohol use, while the other half of the participants received an additional section on smoking, social networks, and health. All participants also received questions on their use of drugs (108).

The study sample for the 2011 Danish National Alcohol and Drug Survey was drawn from the Danish Civil Registration System. To be included in the Danish Civil Registration System, an individual must meet at least one of the following requirements: have been born to a mother who is already registered in the system; have their birth or baptism registered in the Danish church register; or legally reside in Denmark, with a place of residence, for longer than three months (133, 165). From the initial sample of 8,004 residents (ages 15–79) randomly selected from the Danish Civil Registration System who received an invitation, 5,133 (64%) participated in the 2011 survey (see Table 2 for description of the respondents and comparison with the Danish population ages 15-79).

The population for Study 2 consisted of the 5,126 respondents who provided sufficient information in the survey to calculate AUDIT-C scores (66). The population for Study 3 consisted of the 4,522 respondents who were not lifetime abstainers, provided information for all 10 AUDIT items in the survey, were of Danish origin, and had no previous history of hospitalization related to alcohol (see Figure 2).

Different exclusion criteria were applied in the two cohort studies due to the different measures and analyses used in each study. As Study 3 used the full AUDIT as an exposure measure, it was necessary that respondents supplied information for all AUDIT items, while for Study 2, only information for the first three AUDIT questions was needed. As well, since Study 3 used survival analysis, looking at time to incident alcohol-related hospital admission,
it was necessary to exclude all respondents with prior hospital admissions for alcohol-related conditions, as well as those respondents for whom full medical histories might not be available. Statistics Denmark (166) distinguishes individuals who are of Danish origin from individuals who were born abroad to non-Danish-citizen parents (i.e., immigrants) and individuals who were born in Denmark to non-Danish-citizen parents (i.e., descendants). As immigrants and descendants are more likely to have spent prolonged periods outside of Denmark, and, therefore, may have hospital admissions not reflected in the Danish registers, the population for Study 3 was restricted to those of Danish origin.

| | Participants (%) | Danish population (%) ^d |
|--|------------------|---|
| Gender | | |
| Male | 2,423 (47.20%) | 2,164,888 (49.92%) |
| Female | 2,710 (52.80%) | 2,172,148 (50.08%) |
| Age | | |
| 15-29 | 1,140 (22.21%) | 1,005,473 (23.18%) |
| 30-45 | 1,308 (25.48%) | 1,222,645 (28.19%) |
| 46-64 | 1,823 (35.52%) | 1,403,642 (32.36%) |
| 65+ | 862 (16.79%) | 705,276 (16.26%) |
| Ethnicity | | |
| Danish origin | 4,787 (93.26%) | 3,882,910 (89.53%) |
| Immigrant | 292 (5.69%) | 401,885 (9.27%) |
| Descendant | 54 (1.05%) | 52,271 (1.21%) |
| Highest level of education as of 2011 ^{a,b,c} | | |
| Low | 993 (21.65%) | 1,170,643 (30.24%) |
| Medium | 2,116 (46.14%) | 1,626,557 (42.02%) |
| High | 1,477 (32.21%) | 1,074,103 (27.75%) |

Table 2. Description of 2011 Danish National Alcohol and Drug Survey respondents (N=5,133) and 2011 Danish population age 15-79 (N=4,337,036)

^a Only includes those aged 15-69 to ensure comparability with population data (survey respondents=4,586; Danish population=3,871,303)

^bData missing for 94 respondents and 92,875 members of the Danish population

°Respondent data are self-reported; population data are based on education registers

^dSource[:] Statistics Denmark - statbank.dk

Each person registered in the Danish Civil Registration System is assigned a unique personal identification number, which allows for linkages between different registers in Denmark (167). This number also made it possible to link respondents' 2011 survey data and Danish register data. In Study 2 and Study 3, data from the 2011 survey were linked with longitudinal hospital records contained in the Danish National Patient Register (132). For censoring purposes, additional register data on date of death and emigration on the cohort members were extracted. Mortality data were drawn from the causes-of-death register (131), and emigration status was determined based on presence in the population register with the date of emigration out of Denmark assigned as December 31st of the year after which they last appeared in the register (168) (Study 2) or the date when a respondent departed from their last residential address in Denmark based on the Changes of Address Register (Bopælsændringer) (Study 3).

Measures

Exposure

In Study 2, exposure status was determined based on AUDIT-C scores, and, in Study 3, both the AUDIT and AUDIT-C scores were used. The 10 AUDIT items were included in the 2011 Danish National Alcohol and Drug Survey. However, as the survey included both beverage-specific and general consumption questions, and because the survey response options were slightly different than those in the original screening tool, some recoding of the survey data was necessary in order to generate AUDIT scores, as is common when the AUDIT is embedded in a larger national survey (e.g., 169, 170); for instance, a survey may include beverage-specific questions because researchers want to study types of beverages consumed, or a researcher may be interested in more fine-grained categories of drinking frequency than are provided in the AUDIT. The method of recoding Danish national survey data described in this section has been used previously to generate AUDIT scores (171).

In the full AUDIT, respondents score between 0–4 points for each item, giving a total minimum score of 0 and a maximum score of 40 (Table 3). The AUDIT-C, which consists of the first three AUDIT items, is scored on a scale of 0–12 points (66). In the original AUDIT, Questions 1–8 offer five response options, and questions 9 and 10 offer three response options.

Figure 2. Flow diagram of participants in the cohort studies



Note: Some individuals were excluded from Study 3 for multiple reasons and are included in all relevant categories.

AUDIT question 1 asks "How often do you have a drink containing alcohol"? The 2011 survey contained this question on general alcohol consumption but also similar beverage-specific questions (e.g. "How often over last 12 months, on average, have you been drinking beer?"). For both the general and beverage-specific questions, nine response options were provided in the survey: 1. "Pretty much every day" 2. "Four to five times a week" 3. "Two to three times a week" 4. "About once a week" 5. "Two to three times a month" 6. "About once a month" 7. "A few times in the last 12 months" 8. "Once in the last 12 months" and 9. "Not for the past 12 months". These response options were collapsed to correspond to the response options in AUDIT question 1 (i.e., "Never" (survey response option 9), "Monthly or less" (survey response options 6-8), "Two to four times a month" (survey response options 4 and 5) "Two to three times a week" (survey response option 3) and "Four or more times a week" (survey response option 1 and 2). The maximum of the general and beverage-specific responses was used. If a respondent did not answer AUDIT question 2, ("How many drinks containing alcohol do you have on a typical day when you are drinking"?), the number of reported drinks consumed during the last drinking occasion was used.

AUDIT question 3 ("How often do you have six or more drinks on one occasion"?) assumes a standard drink equaling 10 grams of pure alcohol (63), giving a total of 60 grams of pure alcohol per drinking occasion. In Denmark, a standard drink is defined as 12 grams of pure alcohol (172). Therefore, the survey question was adjusted to be "five or more drinks". If this question was not answered, beverage-specific and general questions on average number of drinks consumed per occasion and drinking frequency were used to estimate this item. That is, if a respondent replied that, on average, they drank five or more drinks containing beer, wine, spirits, fortified wine, cider/alcopops, or any alcoholic beverage, then the average frequency of drinking that beverage was used. The nine response options listed above, plus a tenth option (10. "Did not have five or more drinks per occasion"), were recoded to correspond to the AUDIT question 3 responses: (i.e., "Never" (survey response options 9 and 10), "Less than monthly" (survey response options 7 and 8), "Monthly" (survey response options 5 and 6) "Weekly" (survey response options 3 and 4) and "Daily or almost daily" (survey response options 1 and 2).

AUDIT questions 4 through 10 were asked consecutively in the 2011 survey. For questions 4 through 6, separate survey response options for "Daily" and "Almost daily" were collapsed to correspond to the AUDIT option "Daily or almost daily." For question 10, the survey response options were "No," "Yes, once," and "Yes, more than once". Otherwise, the questions and responses replicated the AUDIT instrument.

In Study 2, the AUDIT-C was chosen as the exposure measure rather than the full AUDIT to avoid confounding study exposure and outcome. As shown in Table 3, items 4–7 of the full AUDIT measure dependence on alcohol and negative consequences of drinking, including whether the respondent has been injured as a result of their drinking. Since this could overlap with the outcome in this study, only the consumption questions (i.e., the AUDIT-C) were used as the indicator of hazardous drinking. This ensured that the exposure and outcome variables were distinct.

In Study 2, the AUDIT-C was used as a dichotomous variable with a cutoff of five and also as a continuous variable. In Study 3, the AUDIT and the AUDIT-C were used as dichotomous variables, with cutoff points of eight and five, respectively. For the full AUDIT, the cutoff point recommended by the developers was used (63, 64), and for the AUDIT-C, the cutoff point was selected based on a previous general population study carried out in Germany, a neighboring country (173). Although some studies have found that different cut-

offs are appropriate for men and women (174-176), the sources used for Study 2 and Study 3 (63, 64) (173) and current WHO guidance on the use of AUDIT and AUDIT-C in clinical settings do not recommend gender-specific cutoffs (65, 177).

Outcomes

In both Study 2 and Study 3, the outcome was defined and measured using Danish hospital register data. The outcome of interest in Study 2 was the number of hospital admissions due to violence, and, in Study 3, the outcome was time to first hospital admission for ARDD. Thus, the outcome for Study 2 was a count variable (i.e., total number of admissions), while, for Study 3, the outcome was incident cases. These data were identified through data linkage with the Danish National Patient Register (132).

The National Patient Register contains information on all patient contacts with hospital departments in Denmark. This consists of administrative and diagnostic individual-level data, which are updated regularly. The National Patient Register was established in 1977, and, since 1995, has also included information from emergency departments, psychiatric departments, and outpatient clinics (151). Since 1994, the National Patient Register has used ICD-10 codes to specify the primary diagnosis in relation to the hospital contact and, in relevant cases, additional diagnoses (132).

For Study 3, these ICD-10 codes were used to identify hospital admissions for ARDD. The specific diagnoses codes followed those recommended for Swedish register studies (45) and which are used in the National Patient Register (178) (Table 4). The fully alcoholattributable codes identified by Bergman et al. (45) were used because they were inclusive and were specifically recommended for use in register-based studies.

Using the admission date specified in the National Patient Register, it was determined if the ARDD diagnosis occurred prior to or subsequent to the survey. An incident ARDD diagnosis was defined as one that occurred after 1 September 2011. This incident diagnosis formed the outcome variable for Study 3. A prior ARDD diagnosis was one that occurred between 1 January 1994, when ICD-10 codes were first implemented, and 31 August 2011, the approximate date preceding the survey. Prior ARDD diagnoses were used as an exclusionary variable.

In addition to diagnostic information, the National Patient Register also includes an entry stating the reason for the hospital admission for emergency room contacts (132), which is

assigned by emergency department staff. These entries were used to define the outcome for Study 2. Reason-for-contact codes include the following: Illness without direct relation to external lesion; Accident; Act of violence; Suicide, suicide attempt, or self-inflicted harm; Sequelae. As regards the categorization of admissions for violence, the Nordic Medico-Statistical Committee (NOMESCO) Classification of External Causes of Injuries (NCECI) (179) is used in the National Patient Register, whereby violence is defined as "assault by other person resulting in injury" (p. 17), including assault, brawl, maltreatment, and sexual assault (180).

In Study 2, the outcome was any hospital admission with a reason for contact specified as violence during the eight-year follow-up period. All relevant admissions were included, and, thus, the outcome was a count of the total number of admissions that included violence as a reason for contact during the follow-up period. If multiple admissions occurred on the same day, however, these were collapsed into a single episode.

| | | Points and response options | | | | |
|------------|---|-----------------------------|----------------|-------------------------------|--------------------|---------------------------|
| AUDIT item | | 0 | 1 | 2 | 3 | 4 |
| 1. | How often do you have a drink containing alcohol? | Never | \leq Monthly | 2-4 times/ month | 2-3 times/ week | \geq 4 times a week |
| 2. | How many drinks containing alcohol do you have on a typical day when you are drinking? | 1 or 2 | 3 or 4 | 5 or 6 | 7-9 | ≥10 |
| 3. | How often do you have six or more drinks on one occasion? | Never | < Monthly | Monthly | Weekly | Daily or almost daily |
| 4. | How often during the last year have you found that you were not able to stop drinking once you had started? | Never | < Monthly | Monthly | Weekly | Daily or almost daily |
| 5. | How often during the last year have you failed to do what was normally expected from you because of drinking? | Never | < Monthly | Monthly | Weekly | Daily or almost daily |
| 6. | How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? | Never | < Monthly | Monthly | Weekly | Daily or almost daily |
| 7. | How often during the last year have you had a feeling of guilt or remorse after drinking? | Never | < Monthly | Monthly | Weekly | Daily or almost daily |
| 8. | How often during the last year have you been unable to remember what happened the night before because you had been drinking? | Never | < Monthly | Monthly | Weekly | Daily or almost daily |
| 9. | Have you or someone else been injured as a result of your drinking? | No | | Yes, but not in the last year | | Yes, during the last year |
| 10. | Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down? | No | | Yes, but not in the last year | | Yes, during the last year |

Table 3. Alcohol Use Disorders Identification Test (AUDIT) items and scoring scheme

Note: Adapted from Babor et al. (63).

Table 4. Included alcohol-related diagnoses and International Classification of Diseases

 (ICD-10) codes

| Diagnosis | ICD-10 code |
|--|-------------|
| Alcohol-induced pseudo-Cushing syndrome | E24.4 |
| Mental and behavioral disorders due to use of alcohol | F10 |
| Nervous system injury/disease due to alcohol | G31.2 |
| Alcoholic neuropathy | G62.1 |
| Myopathy due to alcohol | G72.1 |
| Alcoholic cardiomyopathy | I42.6 |
| Gastritis due to alcohol | K29.2 |
| Fatty liver due to alcohol | K70.0 |
| Alcoholic hepatitis | K70.1 |
| Liver fibrosis and liver sclerosis due to alcohol | K70.2 |
| Liver cirrhosis due to alcohol | K70.3 |
| Liver failure due to alcohol | K70.4 |
| Unspecified liver injury due to alcohol | K70.9 |
| Acute pancreatitis due to alcohol | K85.2 |
| Chronic pancreatitis due to alcohol | K86.0 |
| Maternal care for (suspected) damage to fetus from alcohol | O35.4 |
| High blood levels of alcohol | R78.0 |
| Toxic effect of ethanol | T51.0 |
| Toxic effect of alcohol, unspecified | T51.9 |
| Alcohol deterrents | Y57.3 |
| Intentional self-poisoning by and exposure to alcohol | X65 |
| Alcohol rehabilitation | Z50.2 |
| Alcohol abuse counselling and surveillance | Z71.4 |
| Lifestyle problems due to use of alcohol | Z72.1 |

Covariates

Additional variables identified as relevant for the present studies based on prior research (showing them to be associated with both alcohol screening scores and violence or ARDD) were selected from the 2011 survey and from the Danish registers. In both Study 2 and Study 3, gender (20, 181-189), age (20, 181-187, 189-193), highest level of education (20, 183, 185, 186, 191, 193, 194), and prior psychiatric disorders (187, 191, 195-200) were included in the analyses. Study 2 included four additional variables: ethnicity (182, 188, 190, 201), presence of minor children in the home (191, 192, 201), cohabitation status (181, 189, 191, 192, 201), and past-year illicit drug use (191, 194, 200, 202).

In Study 2 and Study 3, age was included as a continuous variable (separated in decades in Study 3) in the regression analyses and as a categorical variable with four groups (i.e., 15-29 years, 30-45 years, 46-64 years, and 65+ years) in the descriptive analyses. Gender was coded as male or female based on the participant's 2011 survey response. In Study 2, the

participant's highest level of education was identified using the Highest Completed Education register from 2018 (203) and in Study, 3 was identified using the participant's 2011 survey response. Highest level of education was grouped as follows: low (compulsory education or less), medium (vocational or upper secondary education), and high (higher education). Danish education registers have been demonstrated to have high validity and coverage (203). For the interaction analysis in Study 2, level of education was dichotomized (low and medium versus high). A prior psychiatric disorder was defined as an F2 (schizophrenia, schizotypal and delusional), F3 (mood), F4 (neurotic, stress-related and somatoform), or F6 (adult personality and behavior) ICD-10 diagnosis in the National Patient Register prior to 1 September 2010 (Study 2) or 1 September 2011 (Study 3).

For Study 2, ethnicity was included as an additional covariate, while, for Study 3, non-Danish ethnicity was used as an excluding variable. Ethnicity was drawn from the population register and was defined based on the standard definitions used by Statistics Denmark: individuals who were of Danish origin, immigrants, or descendants.

Study 2 included a measure of whether there were minor children (< 18 years) living in the respondent's home in 2011 and was determined based on responses to the 2011 survey. Study 2 also used the respondent's prior illicit drug use as a covariate, and this information was identified from the 2011 survey. A respondent was considered to have used illicit drugs if they replied in the survey that they had used cannabis resin, cocaine, amphetamines, ecstasy, solvents, hallucinogens, heroin, or other opiates (methadone, opium, or morphine) in the past 12 months. In terms of cohabitation status, respondents were considered to be living with a partner if they either reported they were married/living with a partner in the 2011 survey or if they were registered as part of a couple in the population register as of 2011, using the standard definition of Statistics Denmark (204). Statistics Denmark defines a couple as individuals who a) are married, b) are in a registered partnership, c) are cohabitating and have at least one common child, or d) are cohabitating, are of different sex, are not in a close family relationship (e.g., not siblings), and have less than a 15-year age difference.

Statistical analyses

For Study 2, participants were initially divided into two groups: AUDIT-C score of 0–4 and AUDIT-C score of 5 or higher. In order to assess a dose-response relationship, analyses were also conducted with AUDIT-C total score and scores for each of the three AUDIT-C items (separately) as continuous variables.

For Study 3, as in Study 2, an AUDIT-C cutoff of 5 was used to divide participants. As well, participants were divided into two groups using a total AUDIT cutoff of 8 (AUDIT score of 0–7 and AUDIT score of 8 or higher).

Survey respondents were followed using register data, beginning 1 September 2010 for Study 2 and 1 September 2011 for Study 3. At the time of the project application, register data on the cohort were available through 2018. In Study 2, follow-up continued until the end of the study on December 31, 2018, emigration, or death, whichever came first. In Study 3, as incident cases were the outcome of interest, follow-up continued until hospitalization for ARDD, emigration, death, or December 31, 2018, whichever occurred first. Initially, in both studies, an overview of the study population was presented, and cross-tabulations with corrected, weighted χ^2 tests were used to examine bivariate associations between AUDIT-C scores (AUDIT-C < 5 vs. AUDIT-C \geq 5) and the covariates in Study 2 and between AUDIT scores (AUDIT < 8 vs. AUDIT \geq 8)/AUDIT-C scores (AUDIT-C < 5 vs. AUDIT-C \geq 5) and the covariates in Study 3.

When an outcome variable is in the form of a count, there are several models that may be appropriate for the analysis. In Study 2, the negative binomial regression, Poisson, and zero-inflated Poisson models were compared using the Bayesian information criterion (BIC) and the Akaike information criterion (AIC) in order to select for the most appropriate fit. Follow-up time was included as an exposure variable in the models, and, in the zero-inflated model, a constant zero-inflation was chosen (205). Based on the BIC and AIC, Poisson regression was selected for multivariable modelling, and incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were calculated.

After testing for main effects, interactions of AUDIT-C with age, gender, and SES were then tested separately in multivariable regressions. If there were significant interaction effects, the predictive margins for the moderating variable were plotted. These graphs showed the relationship between AUDIT-C and predicted number of hospital admissions for violence across levels of the relevant sociodemographic variable.

In Study 3, preliminary analyses included a descriptive of analysis of the incidence rates overall and by AUDIT and AUDIT-C status, which were calculated as the number of new admissions for ARDD divided by 100,000 person-years. The relationship between AUDIT and AUDIT-C scores and time to first hospital admission for an ARDD was initially examined with cumulative hazard curves and then with Cox proportional hazard models,

which were used to calculate hazard ratios (HRs) with 95% CIs. As a sensitivity analysis for the choice of AUDIT and AUDIT-C cutoffs, receiver operating characteristic curves (ROC) were generated, providing sensitivity and specificity of the various cutoff points. Subsequently, additional survival analyses were performed using the optimal cutoff points as indicated by the results of the ROC analysis.

In both studies, regression analyses used weights created by Statistics Denmark that reflect the age, gender, family structure, education, income, and country of origin of the national population. Analyses were carried out using STATA v.16 (206) for Study 2 and STATA v.16 (206) and R (207) for Study 3.

Ethics

Respondents to the 2011 Danish National Alcohol and Drug Survey indicated their consent to participate in the survey by completing the questionnaire. As regards the register data used in the studies, Danish register data are collected and stored for monitoring and quality assurance purposes, and, according to Danish law, no ethics evaluation or informed consent is needed, except for research involving human biological material, in which case, regional ethical committee approval is required (123). In Denmark, the use of personal data from registers is governed by the Data Protection Act. This legislation allows for special use of data for scientific and statistical purposes in cases where "the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant importance to society and where such processing is necessary in order to carry out these studies" (208) (p. 6).

The register-based components of the thesis were approved by Statistics Denmark. In order to access register data housed by Statistics Denmark, a necessary requirement is that the researcher is affiliated with a Danish-based institution that is pre-approved by Statistics Denmark. In the current project, the pre-approved institution was Aarhus University.

The current analyses were an extension of a prior project that had previously been approved by Statistics Denmark. Approval of the application for the current project, which outlined the revised purpose and request for additional data and a new population, was granted by Statistics Denmark in December 2019. The project was registered with Aarhus University and the Danish Data Protection Agency.

SUMMARY OF RESULTS

Study 1

As previously outlined, the aim of Study 1 was to map the existing literature on registerbased studies of alcohol's harms to family members. This involved identifying the methodological features of previous studies, summarizing the main findings and comparing them to findings from survey-based studies, and identifying gaps in the research literature.

As regards the research setting, the studies were conducted in seven different countries. The vast majority (n=78) were carried out in the Nordic region, and the remaining were conducted in Australia, the United States, and Taiwan. Studies were published between 1976 and 2019. The distribution of publication date strongly skewed toward recent years, with 60 of the studies published since 2010 and 44 published since 2015. In terms of the relationship between the drinker and the relative, 79 of the studies (87%) solely examined outcomes for children of heavy drinkers. Two studies solely addressed outcomes for spouses/partners. Seven of the studies examined outcomes for more than one first-degree relative (i.e., children, siblings, parents), and, in three of the studies, the familial relationship was unspecified. Regarding the research focus of the studies and the salience of the relative's substance use in the analyses, familial substance use was the primary explanatory variable under investigation in 23 of the studies; was one of several risk factors explored in 57 studies; and was included as a covariate in the analysis in 11 studies. Studies differed in terms of whether they distinguished between alcohol and drug use as independent risk factors. In 49 studies, heavy drinking was a unique exposure, while the 42 other studies used an exposure variable that combined heavy drinking and illicit drug use.

Various sources were used to assess heavy drinking, but the majority of studies used at least one register. Hospital registers (inpatient and outpatient) were the most common, with 41 studies relying on them as the sole information source. These studies defined a heavy drinker as an individual with a hospital admission for a fully alcohol-attributable condition categorized based on ICD diagnosis codes, including, for example, alcohol abuse, alcohol dependence, alcoholic hepatitis, and/or alcoholic cirrhosis of the liver. Hospital registers were also frequently combined with other registers, such as prescription registers, mortality registers, and criminal registers such that an alcohol-related record in one or more of the registers was sufficient to categorize the individual as someone who drinks heavily. With prescription registers, heavy drinkers were identified in the studies based on the individual's

purchase of prescription medicines for treating/preventing alcohol use disorders, for instance, using the Anatomical Therapeutic Chemical Classification System code N07BB, which is the category of drugs used in alcohol dependence (146, 209). Mortality registers identified individuals with an alcohol-related cause of death. Criminal registers, which recorded substance-related crimes, such as driving under the influence of alcohol, were also used to identify heavy drinkers. Informant reports as the sole information source were used by 13 studies, as when respondents were asked to report whether a family member was a heavy drinker. For instance, respondents were asked, "When you were growing up, that is, during the first 18 years, did you live with anyone who was a problem drinker or alcoholic?" (210), or were asked to rate their father's alcohol habits (drinking frequency) on a Likert scale, ranging from (1) never (consume alcohol) to (4) often (211).

The outcomes assessed in the studies covered a broad range of areas, which could be grouped into the overarching themes of mental health, mortality, criminal activity, employment/financial, physical health, out-of-home placements, suicide attempts, education, receipt of child welfare measures, abuse/neglect, adolescent pregnancy, and military fitness. As some studies addressed multiple outcomes, the total number of outcomes exceeded 91. Outcomes falling under the category of mental health were the most commonly explored, with mortality and criminal activity also frequently investigated. Mental health outcomes were defined using diagnoses of mental disorders recorded in inpatient or outpatient medical registers or based on the purchase of a medication used to treat a mental disorder recorded in a prescription register. Some studies assessed risk of any mental disorder, while others assessed particular diagnoses, such as mood disorders, behavioral and emotional disorders, schizophrenia, schizotypal and delusional disorders and psychosis, eating disorders, neurotic disorders, disorders of psychological development, and mental retardation. Mortality was defined using deaths recorded in a cause-of-death register. Some mortality studies had particular focus on suicide or sudden infant death syndrome and other causes of post neonatal death, while the majority assessed risk of all-cause mortality. Outcomes in the category of criminality were defined using convictions identified in a criminal offenses register, with some studies addressing specific categories of crime (e.g., violent crimes) and others looking at risk of recidivism.

Employment/financial outcomes, physical health conditions, and out-of-home placements each accounted for approximately 10% of the studies. Employment/financial outcomes were defined as a record in a labor market participation register or social insurance register which

indicated a period of unemployment or the receipt of social benefits or disability pensions. For outcomes that fell under the category of physical health, studies often operationalized these as an inpatient or outpatient hospital admission for an injury or disease (using a specific ICD diagnosis code) that was recorded in a patient register. Physical health outcomes were also defined by some studies using records in a clinical disease register or records of sick leave in a national health insurance register. Other outcomes identified in the scoping review are summarized and described in the online supplementary materials published with the Study 2 article.

Further analyses were conducted on the 23 studies that had familial substance use as the primary exposure under investigation. These were studies in which heavy drinking was the main explanatory variable, alone or in combination with illicit substance use. In summarizing the findings, the terms "heavy drinking" and "substance use" are used broadly; however, in the individual studies, other terms may have been used by the authors.

The scoping review identified five studies that investigated risk of mental disorders (as a general category), and four of these found some measure of increased risk for children of parents with substance use (146, 212-214); however, some qualifications should be noted. In one of these studies, the findings depended on the age of the child, such that parental substance use was associated with an increased the odds of mental disorders during the adolescent period but not in mid-childhood (212). In another study, there were sex differences such that maternal less severe and severe heavy drinking increased children's risk of mental and behavioral disorders; however, for fathers, only severe heavy drinking was associated with an increased risk (146).

Two studies examined infant and child mortality, and both found an increased risk of offspring death during the study periods among children of mothers with heavy drinking (215, 216). Two of the four studies that investigated mortality among young adults and adults found that risk of death during the follow-up period was higher among family members of heavy drinkers (148, 210). Among the 23 studies with substance use as the primary explanatory variable, Rogers et al. (210) was the sole study to explore relationships beyond the parent-child dyad. By also analyzing mortality risk associated with childhood exposure to heavy drinking by siblings and other family members, this study could explore dose-response relationships, such as whether the risk of death increased with increasing number of heavy-

drinking family members, years lived with heavy drinkers, and immediacy of the relationship (210).

As regards risk of criminality, five of the six studies found some significant difference in recorded convictions between offspring exposed to parental heavy drinking and offspring who were not (148, 217-220). The earliest study (220) reported that the difference was significant only among male children.

Educational outcomes were explored by three studies, and all found that parental heavy drinking was associated with poorer school performance or attendance (221-223). In one of these studies (221), adjusting the analyses for family psychosocial circumstances greatly reduced the effect size for parental heavy drinking.

Two studies investigated the relationship between parental heavy drinking and risk of abuse/neglect of offspring. The results of one of these studies indicated that parental heavy drinking was associated with an elevated risk of offspring violence victimization (148), and the other study found that parental heavy drinking was associated with significantly increased odds of child maltreatment (136).

All of the studies assessing risk of placement in residential or foster care found significant differences between children of heavy-drinking parents and controls (136, 144, 148, 219, 220, 224). Sex differences were identified in two early studies such that a significant difference was only observed among male children (220, 224). Substance-specific effects were explored by Raitasalo et al. (144), who found that combined maternal heavy-drinking and illicit drug use was associated with the highest risk of out-of-home placements.

The four studies investigating the relationship between parental substance use and risk of physical illness and injury hospitalizations among offspring all showed a significant positive association (144, 214, 225, 226). Substance-specific analyses by Raitasalo et al. (144) again found the highest risk for combined maternal heavy-drinking and illicit drug use.

Study 2

Study 2 linked exposure data consisting of AUDIT-C scores collected from the crosssectional 2011 Danish National Alcohol and Drug Survey with outcome data on respondents' violence-related hospitalizations from the National Patient Register over eight years in order to examine the relationship between hazardous drinking and subsequent risk of violence victimization. A further aim involved examining whether sociodemographic variables moderated the relationship between hazardous drinking and violence-related hospitalization.

The average duration of follow-up in Study 2 was 8.1 years. During follow-up, 51 of the respondents (1.2%) had one or more violence-related hospital admissions. Of the respondents with hazardous drinking, 40 had at least one admission (2.0% of those with AUDIT-C \geq 5), and, of the respondents without hazardous drinking, 11 had at least one admissions (0.5% of those with AUDIT-C<5). Multiple admissions were rare. Fewer than five participants experienced two admissions, and none of the respondents were admitted more than two times.

The main effects model in which AUDIT-C was included as a dichotomous variable showed that the rate of hospitalization for violence was 2.28 times higher [95% CI=1.16–4.50] for respondents with hazardous drinking (AUDIT-C \geq 5) compared to those without hazardous drinking (AUDIT-C<5). Increasing age was associated with a lower rate of hospital admission for violence-related causes (IRR=0.94, 95% CI=0.92–0.96). Those with a low level of education had a significantly higher rate of violence-related admissions compared to those with higher education (IRR=3.68, 95% CI=1.56–8.67). The main effects model in which AUDIT-C total score was included as a continuous variable showed that increasing AUDIT-C scores were associated with an increased rate of hospital admission for violence (IRR=1.20, 95% CI=1.06–1.37).

When AUDIT-C score was included as a continuous variable, the results showed a statistically significant interaction between gender and AUDIT-C score on rate of violence-related hospital admission (IRR=0.69, 95% CI=0.53–0.90). The interaction was not statistically significant when the AUDIT-C cutoff was used. Study 2 found that there was no significant interaction between the other sociodemographic variables and AUDIT-C score (continuous or cutoff) on rate of hospitalization for violence.

Figure 3 plots the predictive margins by gender, illustrating the interaction between gender and AUDIT-C. The graph shows a dose-response relationship among male respondents such that increasing AUDIT-C scores, particularly in the higher range, are associated with increased predicted hospital admissions for violence.



Figure 3. Predictive margins by gender (95% CIs) for the interaction between gender and AUDIT-C total score (0-12 points) in Study 3

Figure 3 shows the predictive margins by gender and AUDIT-C score with 95% CIs in Study 3. The predicted number of hospital admissions for violence at each combination of gender and AUDIT-C score are plotted.

Notes: AUDIT-C=Alcohol Use Disorders Identification Test-Consumption; CI=confidence interval; reproduced from Brummer et al. (227)

Study 3

Study 3 linked respondents' AUDIT and AUDIT-C scores from the 2011 Danish National Alcohol and Drug Survey with hospital admission data from the National Patient Register in order to investigate whether AUDIT and AUDIT-C scores are associated with subsequent hospitalization for ARDD during a seven-year follow-up.

In total, there were 56 incident admissions for ARDD among the respondents, with 35 occurring among respondents with high AUDIT scores, and 21 occurring among those with low AUDIT scores. The incidence rates of respondents above and below the AUDIT cutoff were 441.3 and 109.8 per 100,000 person-years, respectively. In terms of incident admissions by AUDIT-C status, 48 of the admissions occurred among respondents with high AUDIT-C scores, and eight occurred among those with low AUDIT-C scores, giving incidence rates of 380.9 and 49.9 per 100,000 person-years, respectively.

The results of the multivariable Cox regression analysis showed that respondents who scored above the AUDIT cutoff of eight and the AUDIT-C cutoff of five had a significantly increased risk of being hospitalized for an ARDD compared to those who scored below the AUDIT and AUDIT-C cutoffs, respectively (AUDIT: HR=4.72, 95% CI=2.59-8.60; AUDIT-C: HR=7.97, 95% CI=3.66-17.31). Sensitivity analyses using alternate cutoffs identified by ROC (AUDIT cutoff of 7; AUDIT-C cutoff of 6) also showed an increased risk of ARDD hospitalization for participants scoring above the cutoffs, with, again, a stronger association for the AUDIT-C (AUDIT: HR=5.86; 95% CI=3.09–11.11; AUDIT-C: HR=6.98; 95% CI=3.69–13.18).

DISCUSSION

The three studies that comprise this thesis have demonstrated how, by comparing, contrasting, and linking two distinct data sources – registers and surveys – our understanding of alcohol's harms to the drinker and to others could be furthered. Study 1 reviewed previous research on alcohol's harms to family members in order to identify methodological features of register-based studies and to examine how findings from such studies, when juxtaposed against survey-based findings, give particular insight into the relationship between heavy drinking and harms to family members. Studies 2 and 3 linked a survey-based alcohol exposure measure and a register-based health outcome measure to assess relationships that had previously not been investigated using this methodology.

Discussion of findings and comparison with previous research

What are the methodological features of existing register-based studies of alcohol's harms to family members? (Study 1)

Although the review placed no restrictions on the source of exposure data, the vast majority of studies operationalized heavy drinking using a register-based exposure measure (e.g., a registration for an alcohol-related condition in a hospital register). Since, in general, only quite severe alcohol problems will lead to an alcohol-related register entry, such as a hospitalization, death, or arrest, this method of operationalizing the exposure, as noted in the Introduction of this thesis, will tend only to identify those individuals at the severe end of the spectrum of harmful and hazardous alcohol use (63, 228).

This way of measuring the exposure relates to another methodological feature in terms of how the association is made between the exposure and the outcome. In solely register-based research, an association between alcohol consumption and outcomes can be established in various ways (118). On the one hand, information about alcohol's role in a particular event may be recorded in the same register as the assessed outcome. In the case of alcohol's harms to family members, for instance, registers of child abuse or protection measures may record parent alcohol use; or criminal registers containing domestic violence incidents may record whether the perpetrator had been intoxicated. An additional way in which an association can be explored is through record linkage of various register data and statistical analyses. In research on alcohol's harms to family members, alcohol exposure can be assessed through one register, such as an alcohol use disorder diagnosis in a patient register; familial relationships can be assessed through a second register, such as a birth register; and outcomes

may be assessed through a third register, such as a foster care placement recorded in a national child welfare register. These registers can then be linked through an individual's personal identification number, and statistical analysis can be carried out to answer a research question concerning whether children of heavy drinkers have a higher risk of foster care placement. The majority of studies identified in the review used this methodology in which a register-based alcohol exposure was linked with an outcome recorded in a different register. Only one study (229) identified in the scoping review used information in which alcohol's role in a particular event was recorded in the same register entry as the assessed outcome. This is consistent with results from a recent review in six countries, which showed that the systematic collection of data on the role of alcohol in an event/case by agencies was rare (230). This type of data may involve a police officer or case worker flagging whether an episode involved alcohol, and unless such decisions are based on predetermined criteria, they can be highly subjective (231).

The cross-source linkage methodology, in which a register-based outcome was linked with alcohol exposure identified and measured using a non-register-based source, was used by a minority of studies identified in this review, and, when applied, consisted mainly of informant reports (e.g., the respondent was asked to rate their father's "alcohol habits (drinking frequency)" on a four-point Likert scale, with a range of (1) never to (4) often" (211)) that were then operationalized into a dichotomous exposure variable, such as "father's alcohol habits yes vs. no" (e.g., 211, 232).

Regarding the outcome measures of the included studies in the scoping review, a previous review by Rossow et al. (233) of cohort studies that investigated non-clinically diagnosed parental alcohol problems and adverse outcomes in children found that only 12% of studies (n=16) assessed outcomes that were not defined as related to substance use. Therefore, it is striking that Study 1 identified 91 register-based studies covering a range of non-substance-related outcomes for family members, including physical/mental health, mortality, criminality, and education/employment. This likely reflects the proliferation of research in this area in the past few years as well as differences in the exclusion criteria between the review by Rossow et al. (233) and Study 1, with Study 1 tending to focus on the effects of clinically diagnosed alcohol use disorders.

In addition to covering a large number of categories, the outcomes examined by studies in Study 1 varied in terms of their temporal links to drinking. For example, placement in foster

care or physical abuse could be a more immediate consequence of childhood exposure to familial substance use. On the other hand, adult mortality or economic outcomes are temporally more distant.

A final methodological feature of interest in the scoping review was the familial relationship examined by the studies. Study 1 identified that, for the most part, children of heavy drinkers have been the focus of existing register-based studies. Register-based studies' focus on the parent-child relationship may be a byproduct of the fact that conducting survey research on children is especially challenging (234). Researchers may have found register data suitable for investigating alcohol's harms to children since, as opposed to surveys, this method uses existing data and does not require contact with the research subject. Research on alcohol's harms to children is complicated by the challenges of separating out socialization from genetic mechanisms. However, since register-based studies can easily distinguish between "lived with" versus "not lived with" parents (as recorded and tracked over time in population registers), they are well-suited to explore this issue, and this may also explain the preponderance of parent-child-focused register research on this topic. On the other hand, research on alcohol's harms to spouses and partners is associated with challenges that are not so easily addressed by registers. For instance, research on spouses and partners is complicated by mechanisms of assortative mating and convergence. Assortative mating refers to the fact that, quite obviously, people are not randomly assigned to romantic partners, but, rather, tend to become involved in relationships with people with whom they have, for example, shared traits, lifestyles, and experiences, including similar drinking behaviors and mental health status (235-237). Convergence refers to the fact that people's behaviors and traits become more similar over the course of a relationship (237, 238). These mechanisms pose a challenge when determining causal pathways. For instance, as succinctly described by Rognmo et al. (239), "a negative correlation between alcohol consumption in spouse A and mental health in spouse B could be a secondary result of the statistical relationship between alcohol consumption in spouse A and in spouse B and between alcohol consumption in spouse B and poor mental health in spouse B" (p. 2). While registers can offer some insight into assortative mating with respect to severe alcohol problems (e.g., by examining alcoholrelated diagnoses recorded in hospital registers before a relationship), solely register-based studies cannot easily address assortative mating or convergence in regard to subclinical drinking. This may thus explain why spousal relationships were rarely included in the studies in the review. Another complication of research assessing the partner/spousal relationship, as

opposed to the parent-child relationship, is the frequent and comparatively simple termination of the relationship. While parent-child separation occurs less frequently, and, in cases of forced-removal, only in extreme situations and with significant involvement of government authorities, divorce between partners has become very common. Thus, when investigating the relationship between heavy alcohol use of one partner and outcomes for a second partner, divorce may occur before the outcome would be detected, especially one that would be recorded in a register. Prior studies show that heavy drinking is associated with marital discord (240) and is a predictor of divorce (241). Thus, the combination of these factors could result in a type of selection bias with an overrepresentation of, for example, couples with particular drinking behaviors or partners with certain characteristics that make them less likely to divorce a heavy-drinking spouse. In summary, there may be various methodological explanations for why parent-child research dominated the register-based studies identified in Study 1, while research on other family members, and spouses in particular, was sparse.

What are the main findings of register-based studies of alcohol's harms to others, and how do the findings differ from those of survey-based studies, if at all? (Study 1)

Study 1 showed that register-based studies of alcohol's harms to family members have found that children of very heavy drinkers are at an increased risk for physical and mental health problems, poor educational outcomes, family separation, abuse/neglect, infant/child mortality, and later criminality. General population surveys have investigated some of the same harms (for instance, physical health and abuse/neglect) as those assessed by the register-based studies included in the scoping review. In a survey-based study, a relationship between heavy drinking and harm to a child might be assessed using the following question: "In the last 12 months, has one or more of the children who you are responsible for . . . been left in an unsupervised or unsafe situation/been yelled at, criticized or otherwise verbally abused/been physically hurt/witnessed serious violence in the home . . . because of someone's drinking?" (21). As was discussed in detail in the introduction of the thesis, such a question presupposes a causal link between heavy drinking and the outcome. In addition, the wording requires a subjective interpretation by the respondent. For example, there could be different interpretations of an "unsafe situation" or of being "criticized," and, as Room et al. (22) argue, "perceptions and thresholds" may differ between individuals, groups, and cultures. As well, because consequences of family members' heavy drinking may cover sensitive areas, there is a risk that respondents in a survey study may underreport these outcomes (242). Register-based research, however, does not rely on self-reports, and, as demonstrated by

Study 1, uses a different approach to investigate alcohol's harms to others. For instance, outcomes in the domains of physical and mental health may be operationalized as a hospital admission with specific ICD diagnostic codes recorded in a patient register (214), and the association between the outcome and a family member's heavy drinking is investigated by linking registers.

Previous reviews covering largely survey-based studies have also shown that parental substance use is a risk factor for children's psychosocial problems (141, 233, 243). However, focusing exclusively on register-based studies, Study 1 offers a different perspective and highlights the utility of drawing on register data. As demonstrated by Study 1, register-based studies can inform on very specific harms, such as whether children of heavy drinkers are at greater risk of a particular disease or disorder (144, 146, 225). In addition, as mentioned previously, register data permits long follow-up, and, thus, through registers, an individual can be tracked through all stages of life – from birth to death. Consequently, both the short-term and long-term impact of exposure to a family member's heavy drinking present at birth (or even prenatally) or during early childhood can be assessed, as well as exposures that occur at different stages of development. For example, Martikainen et al. (213) examined the effects of repeated exposures to parental substance use at three different stages of childhood, with an increased number of periods indicating higher levels of exposure.

Others reviews that have not drawn on register studies have mainly explored the adolescent stage, or internalizing and externalizing problems among children (233, 243). Study 1, however, could investigate the breadth of the impact of alcohol's harms to children since register-based studies address, for example, many different physical and mental health outcomes and also include study populations consisting of young children (e.g., (214, 225)).

In a systematic review looking at whether parental drinking influences children's drinking, Rossow et al. (244) found that most studies on the subject were not guided by theory-driven hypotheses, which they cite as a key criterion for establishing a causal relationship. Although a quality assessment of the included studies' methodologies was not part of Study 1, some features of register-based studies were identified which could facilitate the testing of theory-based hypotheses and contribute to demonstrating a causal relationship between heavy drinking and harm to a family member. For instance, some studies have investigated whether fetal exposure to alcohol (although not the focus of the scoping review) and the resulting effects on physical and mental development could represent a causal

pathway from maternal alcohol consumption to child harm (e.g., poor school achievement) by using register data to establish the timing of an alcohol use disorder diagnosis relative to pregnancy (e.g., (222)). Other studies attempted to isolate socialization from genetic mechanisms by differentiating between "lived with" versus "not lived with" immediate family members or to control for confounders by including fixed sibling effects (213, 214, 218) – these types of analyses are facilitated by population registers which link family members and provide regularly updated detailed information on household composition.

What are the gaps in the literature of register-based studies of alcohol's harms to family members? (Study 1)

Study 1 pointed to some ways in which alcohol register-based research has thus far been underused. Existing register-based research on alcohol's harms to family members has focused overwhelmingly on the parent-offspring relationship. As mentioned previously in the Discussion, there are numerous methodological explanations why register-based research has been skewed toward children and, for instance, spouses, have been neglected. Nonetheless, particularly in the Nordic countries, first-, second-, and even third-degree relatives can easily be linked using personal identification numbers and population and birth register if the births do not precede the establishment of the register (245, 246). Thus, there appears to be a wealth of available data that could be used to explore alcohol's harms to parents and siblings, for example.

One gap in the literature concerns the linking of register-based outcome sources with other non-register-based alcohol exposure sources. Using surveys for exposure data presents the chance to examine drinking levels that may be harmful but not extreme enough to be recorded in a register and to assess dose-response relationships; however, given the few studies that incorporated survey data, it appears that the cross-source linkage methodology is a substantially underused approach.

Although focused on harms to the drinker, Studies 2 and 3 contributed to filling this gap in the literature by linking alcohol exposure data taken from the 2011 Danish National Alcohol and Drug Survey in the form of AUDIT and AUDIT-C scores with longitudinal hospital records contained in the Danish National Patient Register.

Is hazardous drinking as measured in a general population survey sample associated with a subsequent increased rate of hospitalization for violence? (Study 2)

Study 2 found that hazardous drinking was associated with an increased rate of subsequent hospital admissions for violence-related causes in a general population sample. This is consistent with findings from prior studies using emergency department samples, which showed that intoxicated patients were at higher risk for suffering violence-related injuries than non-violence-related injuries (247, 248), as well as case-control (using population control) and case-crossover studies showing that alcohol consumption and dependence are associated with intentional injury (50, 249). They are also in line with results from cross-sectional general population surveys in Denmark showing that drinking at an amount exceeding the high-risk drinking levels set by the Danish Health Authority was a risk factor for self-reported experience of violence (250). Work on alcohol's harms to others has also shown that frequency of intoxication and volume of alcohol consumption are positively associated with one's risk of being physically victimized by someone who has been drinking (106, 251). As well, the results from Study 2 are in line with results from a meta-analysis of alcohol toxicology findings looking at the most severe form of violence victimization, which showed that nearly half of homicide victims tested positive for alcohol, and approximately one third were intoxicated at the time of death, with similar results across geographic locations (252).

Observed relationships between alcohol consumption and victimization may be attributed to cognitive and behavioral disturbances on the part of the intoxicated individual, which increase their risk of experiencing violence (253). For instance, because of alcohol-related impairment, intoxicated persons may be considered "easy targets," or they may irk others, act impulsively or fail to respond to cues in ways that increase their likelihood of being a victim of violence (253). Intoxicated individuals may also be more likely to be in settings and out during times of day that put them in a higher risk for experiencing violence (254). Some of these explanations, such as impulsivity and increased opportunity for experiencing violence due to high-risk locations, could mediate the relationship between alcohol and violence. However, as discussed subsequently in the Methodological considerations section, they may also be considered confounders.

It should also be noted that Study 2 used usual drinking behavior to define the exposure – not drinking in the event. Study 2 lacked information to connect the exposure proximally to the outcome, via, for instance, BAC test results at hospitalization. However, previous

research has found self-reported usual consumption (particularly frequency of drinking and number of drinks per drinking occasion) is positively associated with BAC at hospital admission in injured emergency room patients (255). Furthermore, measure of usual drinking behavior, such as was used in Study 2, may have an advantage over BAC measures recorded in emergency room studies since "time dependent BAC attenuation" may influence results (255). That is, violence-related injuries are generally more serious than other injuries and therefore require quicker treatment, whereas there may be a longer delay (at which point BAC has diminished) between the incident and treatment for individuals with less serious, non-violence related injuries (255).

The results from Study 2 indicate that violence-related hospitalizations are a rare outcome for members of the general population – approximately 1% of the participants had a violencerelated hospitalization during the follow-up. As previously argued, this surely underestimates the overall experience of violence in the population, as only some episodes of violence lead to hospitalization. Analysis of the Danish National Health Survey 2021 (participants aged \geq 16 years) data showed 2.4% of women and 2.2% of men reported that they had experienced physical violence within the last year (256). In this survey, physical violence was defined as "(a) Being pushed, shaken or lightly struck (b) Being kicked, struck with a fist or an object (c) Being thrown against furniture, walls, down stairs or similar (d) Being strangled, assaulted with knife or firearm" (257) (p. 66). In terms of serious violence, defined as the latter three categories, 1.7% of women and 1.6% of men reported experiencing this level of violence in the past year (256). However, it should be noted that even the categories deemed serious, do not necessarily require hospitalization. Based on survey data from 2000 and 2005, it is estimated that approximately 70,000 Danish women aged 16 to 64 years experience physical violence each year, and that 32,000 of these women experience severe physical violence (258). When hospital and police contacts are assessed, it is estimated that 6,000 women are admitted to the emergency room due to interpersonal violence (these figures correspond to nearly 1% of women aged 15 to 19 years), and 5,500 women report violence victimization to the police each year (258). In terms of the overlap in registered cases, approximately half of the women who reported violence to the police also had an emergency room contact for the injuries (258). Looking at specific types of violence in Denmark, it is estimated that the prevalence of intimate partner violence against women reported in surveys is 15 times higher than the prevalence of intimate partner violence based on emergency room contacts recorded in the National Patient Register (259). When Danish national survey data were merged with

national registers, it was found that just 4% of women who reported experiencing intimate partner violence also had a case of violence recorded in the police or hospital register (259). These figures all support the argument that register data represent only a portion of the experiences of violence among members of the Danish population.

Experience of violence is associated with numerous immediate and long-term adverse health outcomes (260). The outcome captured by Study 2 reflects an immediate health consequence of violence. By solely using hospitalization records to measure the outcome, and by defining the outcome as a hospitalization with a reason for contact as violence, Study 2 likely underestimates healthcare contacts due to violence and thus the societal burden of alcohol-related violence. Helweg-Larsen and colleagues, for instance, calculated that Danish women who reported experiencing past-year physical violence had higher healthcare costs (based on primary healthcare contacts, general and psychiatric hospital contacts, and prescription medicine registrations recorded in national registers) in the subsequent year than women who did not experience victimization, and that the difference was largely due to psychiatric treatment (250). Their study, however, could also indicate that psychiatric problems are a risk factor for violence exposure.

Is the relationship between hazardous drinking and later hospital admission for violence moderated by sociodemographic factors? (Study 2)

Study 2 found that gender moderated the effect of AUDIT-C score on rate of violencerelated hospitalizations. The graphs illustrating predictive margins by gender and AUDIT-C as a continuous variable indicated a dose-response relationship for men but not women. Some (261-263) but not all (264-266) prior studies have identified an effect of gender on the relationship between alcohol and physical victimization. In gender-stratified analyses of survey data among older adults in middle- and low-income countries, Clausen et al. (267) found that, when men and women who had consumed alcohol at a high-risk level in the past week were compared to male and female abstainers, respectively, the increased odds of being hit or stabbed was higher among women than men. As regards intimate partner violence, a meta-analysis found alcohol use to be more strongly associated with female victimization than male victimization (268). As well, Rossow and Hauge (269) demonstrated that gender moderates the relationship between a victim's intoxication frequency and physical harm by someone who had been drinking, with a stronger effect for women than men. Other work has shown a stronger influence of alcohol on violence victimization among males than females (270). For instance, in their study of Danish adolescents, Frederiksen et al. (271) found that

alcohol consumption (defined as daily drinking) was associated with violence victimization outside of the home for boys but not for girls. Further, in their analyses of the relationship between alcohol and violent injury in cross-national emergency department settings, Wells et al. (272), found inconsistent evidence for an effect of gender with findings differing depending on the alcohol measure used (i.e., "drinking-in-the-event" or drinking pattern) and country. In terms of gender differences in violence in general in Denmark, survey data indicate that among those ages 16 to 24 years, Danish males have a significantly greater odds of experiencing violence compared to Danish women (OR = 3.2, 95% CI = 2.3-4.2).

Thus, the issue of the role of gender in the relationship between alcohol and violence victimization appears to be complex and likely influenced by cultural factors (e.g., gender differences in drinking prevalence and acceptance of female drinking), socio-demographics (e.g., age), as well as how the exposure (e.g., BAC, usual pattern of drinking, etc.) and outcomes (e.g., being hit/stabbed; "pushed, shoved, hit, or physically assaulted"; "hurt physically and damaged clothes, etc."; in a setting inside or outside of the home) (265, 269, 271) in the studies are defined and measured (e.g., self-reports from general population or from emergency department surveys).

For Study 2, there may be some features of register-based data that can account for the observed interaction effect. Prior studies have found differences between men and women with regard to the settings where they are victimized and the person inflicting the violence, with incidents occurring in the home and partner violence (as opposed to stranger-inflicted violence) more likely among female victims (273-275). Previous research has shown that for instance, 30% of women and just 4% of men who reported experiencing past-year physical violence indicated that the violence was inflicted by a current or former partner (250). Among Danish adolescents, the perpetrator of violence against girls is most often a family member, while, for boys that have experienced violence, the perpetrator is most often an unknown person (271). It may be that these factors, and their influence on whether an episode of violence is recorded in a register, explain the effect of gender observed in Study 2. That is, the observed interaction effect may be attributed to Study 2's methodology and, specifically, to the use of a hospital register to define and measure the outcome. It could be that the types of alcohol-related violence most likely to be recorded in a patient register are episodes that have been witnessed by others (thus prompting calls to an ambulance, for example), such as those occurring in crowded public areas, like bars and pubs. It may be that the alcohol-related violence victimization that women experience occurs and is treated in the home. Since these

incidents are less likely to be observed by third-parties, victims may be less likely to be taken to a hospital, and, thus, these injuries would not be recorded in the hospital register. As well, men may be more likely to suffer serious alcohol-related harms (i.e., those requiring hospitalization) while women are more likely to suffer less severe physical harms (269). Furthermore, stigma associated with intimate partner violence might be a barrier to women seeking treatment for injuries (276).

Study 2 did not find that other sociodemographic variables (i.e., age and SES) moderated the effect of hazardous drinking on rate of hospitalization for violence. Previous studies investigating the relationship between alcohol and other health outcomes have demonstrated an interaction effect for SES (277-279), and the absence of evidence for an effect in Study 2 could partly be due to one of the limitations of using a survey-based sample that was previously noted in the Introduction of the thesis. That is, the study population, which was interviewed by phone or on the Internet, likely did not include certain groups likely to have a high proportion of low-SES individuals (e.g., homeless people), who presumably would also be at high risk of violence victimization.

Are AUDIT and AUDIT-C scores associated with risk for incident hospital admission for alcohol-related conditions in a general population sample over a seven-year follow-up period? (Study 3)

Study 3 found strong associations between both AUDIT and AUDIT-C scores and subsequent hospital admission for ARDD. Thus, the study showed that a self-report alcohol measure from a survey could be informative about the risk of being hospitalized at a later point because of one's drinking. In light of the prominence of the AUDIT and AUDIT-C as screening tools and as measures of alcohol exposure in general population surveys, thorough assessments of the instruments' validity are especially important. By using the cross-source linkage methodology, Study 3 made a significant contribution to this end by demonstrating that these self-reported measures of hazardous and harmful alcohol use can indicate if a member of the general population is at increased risk of developing an ARDD resulting in a hospital admission.

Given the extensive amount of research addressing the AUDIT and AUDIT-C, there are relatively few prior studies investigating whether AUDIT/AUDIT-C scores are predictive of long-term adverse consequences. Findings from the limited work on this topic have, like Study 3, shown that high scores are associated with future negative outcomes. For instance, a longitudinal study from the 1990s demonstrated that a positive AUDIT score was predictive

of self-reported social and medical problems and hospital admissions two to three years after administration of the AUDIT and that the AUDIT's predictive capacity was comparable or superior to laboratory measures (280). A systematic review and meta-analysis of studies assessing mortality risk found that, among drinkers, AUDIT and AUDIT-C scores indicating hazardous drinking were associated with increased mortality risk during a follow-up period of two to 10 years (281). Other research has demonstrated an association between AUDIT/AUDIT-C scores and other subsequent health-related outcomes, such as alcoholrelated gastrointestinal conditions among veterans in the US (282, 283). As outlined later in this Discussion, unlike Study 3, most prior longitudinal studies have not included general population samples and have focused on a limited number of outcomes.

The outcome in Study 3 (ARDD) was quite rare in the population. Whether the AUDIT is an efficient clinical tool to screen for a condition, such as an alcohol use disorder, depends on the prevalence of the condition in the population (284). However, if ARDD is considered to represent the "tip of the iceberg" in terms of alcohol-related health outcomes, with partiallyattributable conditions making up the remainder, and if there is substantial underdiagnoses in hospitals, the findings may support the use the AUDIT or AUDIT-C as a clinical tool to screen for later health harms in a country such as Denmark, where heavy drinking is common. As well, hospitalizations for ARDD are far from a trivial outcome, and, even if uncommon, represent a severe burden at the individual and societal level. In any case, the findings offer another piece of evidence validating the AUDIT and AUDIT-C as important measures of hazardous and harmful alcohol use, including as part of general population surveys.

The multivariable analyses in Study 3 indicated a stronger association between a positive AUDIT-C score and risk of ARDD hospitalization than a positive full AUDIT score at the assessed cutoffs. The results are compatible with cross-sectional studies indicating that AUDIT-C is as effective, or nearly as effective, as the full AUDIT in screening for hazardous drinking in various populations (67, 76, 285-287). Thus, the findings from Study 3 lend further support for the implementation of the AUDIT-C over the full AUDIT in certain situations, such as when time is limited (e.g., emergency departments) (67, 170), or in the context of general population health surveys, where many different topics must be covered, leaving little space for extraneous questions.

Another implication of AUDIT-C's performance in Study 3 is that high-volume drinking, which the three-item tool may be superior at detecting compared to the full AUDIT (66, 288), is distinctly related to later ARDD hospitalization. This would be consistent with considering heavy use to be the defining feature of alcohol use disorders (289). There may be other circumstances, however, in which the full AUDIT may be a more appropriate screening tool. That is, the additional AUDIT questions addressing drinking problems may be relevant to screen for other outcomes, such as harms to family members, or in a clinical population.

A key point is that the specific outcome/endpoint matters when considering the AUDIT and the AUDIT-C (288, 290). When choosing the AUDIT items, the tool's developers prioritized not just results of statistical relationships, but also understandability, cross-cultural validity, relevance for the conceptual domains, and usefulness for prompting discussion as part of a brief intervention delivered by a primary care physician. Thus, the items were selected for specific purposes; however, when used in other contexts, such as measuring excessive drinking among participants in a general population survey, the inclusion of all items may not be desirable. The findings of Study 3 suggest that the consumption items of the AUDIT are strongly associated with subsequent hospitalizations for ARDD in a Danish general population sample and that the additional items may reduce the tool's accuracy in predicting this specific outcome.

A further finding was the high percentage of Danish general population respondents who scored above the AUDIT cutoffs. Approximately 29% of the participants in Study 3 (38% of male and 19% of females) scored above the full AUDIT cut-off of eight. These percentages are considerably higher than figures from other Nordic countries, such as Sweden, where a general population survey conducted in 1997 which found approximately 18% of males and 5% of females (aged 17–71 years) scored above this cutoff (291) and from Norway (aged 18–79 years) where a 2007 survey which showed that approximately 30% of males and 13% females scored above the cutoff (189). However, the proportion of participants above the cutoff (292). Another survey from Finland (conducted in 2007), though, found that approximately 36% of men and 11% of females (ages of 25 and 74) (293) scored about the cutoff. When looking at the mean AUDIT score, Study 3 found a total mean AUDIT score of 6.0 (SD=4.4), with mean scores of 7.2 (4.7) and 5.0 (3.8) for men and women, respectively. Again, these are higher than figures from other Nordic countries, such as Sweden, in which mean AUDIT

scores have ranged from 2.7 to 3.8 for women and from 4.7 to 6.5 for men (76, 294) and from the previously-mentioned 2007 Finnish study, which found a mean AUDIT score of 5.2 (293). The AUDIT scores from Study 3 are also higher than mean AUDIT score of 5.1 for men and 3.3 for women identified based on pooled data from general population surveys in 15 countries (82).

The high proportion of members of the Danish general population scoring at levels indicating hazardous and harmful drinking may reflect genuinely high levels of consumption, heavy episodic drinking, and alcohol problems. For instance, Denmark has a higher total per capita alcohol consumption, which is largely based on sales and taxation data, than most of its Nordic neighbors (295). As well, Danish youth are consistently found to have the highest proportion reporting drinking and intoxication (2, 296). In a study of university students (ages 18–25 years) conducted in 2014, Danish participants had a mean AUDIT score of 9.5, compared to, for instance, participants from Germany and Switzerland, who had a means score of 5.4 and 5.6, respectively (297).

However, differences in AUDIT scores could also reflect that the population surveys were conducted in different time periods, included participants of different ages, used different methods (e.g., questionnaire vs. interview), and may have had different inclusion criteria (e.g., as regards lifetime abstainers, immigrants/descendants, etc.). As well, they likely used different coding structures, as response categories in general population surveys may not exactly correspond to the original AUDIT responses. For instance, the relatively high AUDIT scores in Study 3 may partially be a product of using beverage-specific questions, which tend to result in higher consumption figures (14, 298, 299).

How can register-based research complement survey-based research?

An overall theme of the thesis has been to demonstrate how register and survey data can serve as complementary data sources in investigations of alcohol-related harm. By using general population survey data for the exposure measurement and national register data on hospital admissions due to violence as the outcome measurement, Study 2 explored the alcohol and violence victimization association from a different angle than prior research. As previously discussed in the Introduction, survey questions in alcohol research often contain both the measure of alcohol use and a predetermined alcohol-related outcome (103, 104). That is, the survey question may frame health harms as alcohol-related, and respondents are asked to indicate if they have had such an experience (e.g., "What (were/are) the harmful

effects that you think alcohol (had/has) on your health?" (300). However, in Study 2, through the use of register data, the outcome variable was measured independently of alcohol use – which as mentioned previously, is considered good epidemiological practice and a prerequisite for establishing an association between variables.

By employing register data, Study 2 could also address other limitations of existing studies self-reported experiences of violence. For instance, some researchers have argued for a critical assessment of self-reported morbidity since "the patient's internal assessment may be seriously limited by his or her social experience" (301) (p. 860). For instance, a person living in an environment with a high morbidity prevalence may not identify symptoms/experiences as being noteworthy (301). Survey data are affected by the fact that whether an individual perceives and reports experiences of violence may be affected by, for instance, socio-demographic, cultural, situational and historical factors (258, 302). As well, participants may underreport injuries due to poor recall, especially events that occurred more than six months prior, and may be more likely to underreport "emotionally traumatic events", such as assaults (303, 304).

There are other features of Study 2 and the linked survey-register methodology which are advantageous for addressing the question of whether alcohol is associated with a subsequent increased rate of hospitalization for violence. By using a general population survey-based measure of alcohol exposure, rather than a measure drawn from administrative data (e.g., people with an alcohol use disorder diagnosis), Study 2 could include individuals with less severe heavy drinking, took into consideration different levels and patterns of drinking, and could assess dose-response relationships. As well, by using a patient register to measure the outcome, Study 2 was able to record violence victimization over time, account for multiple experiences of violence by each participant, and avoid the types of nonresponse (305, 306) and, potentially, social desirability bias (307) that may occur when victimization is assessed using surveys.

Study 2 addressed some other weaknesses of past research on the relationship between one's own alcohol consumption and victimization. As argued by Clausen et al. (267), the focus of prior research on acute alcohol consumption, means that the relationship between "overall drinking patterns and risk of injury are less represented in the literature" (p. 126). Thus, by using a measure of alcohol use that reflects usual patterns of drinking, Study 2 contributes to the limited research on associations between hazardous drinking patterns and

violence victimization (267). As well, Study 2 is not prone to the same biases as found in the emergency-department-based studies that serve as the primary source of information on the relationship between alcohol consumption and violence victimization. As Ye and colleagues outline (308), these studies may be affected by selection bias if the geographical area in which the emergency department is located is not representative of, for instance, the rest of the country, or if the emergency department patients are not representative of the hospitalized, as in the Czech Republic, where the most seriously wounded patients are admitted directly to the intensive care units and not the emergency departments, or certain emergency rooms may be specialized to receive certain types of injuries (255). Selection bias in emergency room studies conducted in the United States, for instance, may stem from the fact that emergency room patients contain a disproportionate number of lower SES individuals, since those with better insurance may receive treatment elsewhere (255). Study staff may also systematically seek out or avoid certain types of patients – for example, they may be less likely to approach patients that they deem could be difficult to interview (255). As well, non-response bias is a concern in emergency-department-based studies due to the fact that "non-respondents are more likely to have consumed alcohol before their injury than respondents" (p. 114) (308). Study 2, on the other hand, through the national registers, used data from all emergency departments in Denmark and thus the hospital records are nationally representative. As well, Study 2 uses a general population and not an emergency-department sample. Thus, Study 2 avoids the biases associated with emergency-department studies, although it may suffer from other sources of bias (detailed in the section Methodological considerations below). The fact that findings from Study 2, demonstrating an association between heavy drinking and violence victimization, were consistent with findings from studies using other methodologies demonstrates research triangulation and strengthens the support for an association.

As argued by Helweg-Larsen, a public health researcher, who has worked extensively on describing and analyzing violence in Denmark, different data sources (i.e., population surveys, hospital registers, police registers, and data from shelters) inform about different components of violence since both the type of violence captured and the characteristics of the victims differ (258). Surveys identify incidents respondents perceive (and report) to be episodes of violence, while registers capture incidents that result in contact with public authorities – generally reflecting the most severe episodes. Helweg-Larsen speculates that characteristics of victims identified in registers may also differ from victims identified in

surveys because, for instance, victims with strong social supports may not be as reliant on public authorities. Further, she writes that no one data source is sufficient to provide a description of the victims, but that, when combined, they "provide a relatively complete and up to date image of the magnitude and characteristics of violence against women, as well as the victim and perpetrator profile" (p. 30) (258). The linking of general population survey data on drinking and register data on violence victimization in Study 2 adds further detail to our mapping of this complex topic.

As noted by the findings from Study 1, register-based research is marked by the use of very specific and precisely defined outcomes. This level of available detail will allow register-based studies to make an important contribution to the body of AUDIT and AUDIT-C validation research. Many previous AUDIT and AUDIT-C validations have been carried out, including some longitudinal studies, but there are areas that have remained underexplored. For instance, most studies had not been comprehensive in terms of including all fully alcohol-attributable conditions and have instead focused on selected or partially-attributable conditions, such as gastrointestinal conditions and physical trauma (283). Since Study 3 used longitudinal hospital register data to define and measure the outcome, the full range of specific and precisely defined ARDD (using ICD-10 diagnosis codes) could be included and tracked over a long period.

Survey-based studies, on the other hand, due to space and time restrictions, generally only include the most common health outcomes, or contain vague health-related questions. Health-related outcomes in surveys might be assessed by a non-specific question, such as "Was there ever a time when you felt your drinking had a harmful effect on your health?" (e.g., (309)). As many fully-alcohol attributable conditions are quite rare and may have long induction or latent periods, it would be inefficient to examine the association between AUDIT/AUDIT-C scores and ARDD by a solely survey-based prospective study.

As well, many previous AUDIT validation studies have consisted of special groups, such as veterans or patient populations. By linking AUDIT/AUDIT-C from a general population survey with hospital register data, Study 3 addressed a gap in the AUDIT and AUDIT-C validation literature.

As discussed in the Introduction of the thesis, survey measures of alcohol consumption, as were used in Study 2 and Study 3, have the advantage of providing information on a respondent's level and pattern of drinking as well as identifying less severe forms of

hazardous drinking. Additionally, both studies were able to take advantage of the strengths associated with using register data as an outcome source. For instance, as previously mentioned, Nordic registers have near full population coverage over long periods (134).

Methodological considerations

Selection bias

Study 2 and Study 3

Selection bias is a systematic error that occurs when study participants differ from the target population (310). Selection bias can occur at different points in a study. For instance, in a cohort study, it can occur at the sampling stage if the cohort is not a random sample of the target population, and it can also occur subsequently if response or retention in the study is related to the exposure and the outcome of interest (311).

The sample for the 2011 Danish National Alcohol and Drug Survey, which comprised the cohort used in Study 2 and Study 3, consisted of a random sample of the Danish population from the Danish Civil Registration System and was carried out by Statistics Denmark. However, as was mentioned in the Introduction, sampling frames, such as lists of private households or telephone directories, may exclude or under sample certain groups (15, 19, 112, 113). In order to be included in the sample of the Danish Civil Registration System generated by Statistics Denmark, individuals must have a fixed address and not be on the "address protected" list (approximately 0.5% of the Danish population as of 2015). This means that, for instance, people who are homeless are excluded from the sample. Despite this reservation, however, the risk of selection bias due to non-random sampling in Study 2 and Study 3 is relatively low.

As well, risk of selection bias due to loss to follow-up was also low given that participants did not opt in or out of the register-based follow-up. The outcome variables in both Study 2 and Study 3 were drawn from a medical register with national coverage. The only participants who were not followed until the end of 2018, then, were those who emigrated (using Study 3 definition: n=198) or died (n=93) before the end of the study.

The main risk of selection bias in Study 2 and Study 3 was non-response to the initial survey. The response rate for the survey was over 64%, which was judged to be a "generally good response rate" by the senior journal editor who assessed Study 3. However, it is possible that the responders and non-responders to the 2011 survey differed in ways that
could have affected the validity of the findings of Study 2 and Study 3. As discussed in the Introduction, systematic differences in demographic characteristics and drinking behaviors of study responders and non-responders have been identified by prior studies (112) (114-116); thus, in Study 2 and Study 3, responders and non-responders may have differed in terms of exposure status (i.e., hazardous drinking). As well, it is possible that responders and non-responders in this study may have differed in terms of the outcomes of interest. A study from Finland found that, compared with study responders, non-responders had higher all-cause mortality, with the largest cause-specific mortality differences found for violent and alcohol-related deaths (312). As well, a study from Denmark found a higher risk of alcohol-related morbidity and mortality among non-responders (313). In terms of hospitalizations, another Danish study found small but significant differences between responders and non-responders, but these only were identified in the period immediately preceding and during survey data collection, and not over the long term, and were judged not to have impacted morbidity estimates (314).

For Study 2 and Study 3, weights supplied by Statistics Denmark may have partially addressed the risk of non-response bias, since, in the analyses, responders were weighted to reflect the age, gender, family structure, education, income, and country of origin of the Danish population. However, this method presupposes that individuals within these sociodemographic categories have a similar risk for the exposures and the outcomes (315) and is unlikely to include all characteristics that affect response likelihood (316). Ideally, register data could have been used to assess differences between responders and nonresponders in the 2011 survey, for instance in terms of sociodemographic characteristics and health status (116), and, subsequently, to adjust for non-response to ensure more representative findings. For example, Gottlieb Hansen et al. (111) used register data to adjust for non-participation in the 2005 Danish Health Interview Survey in order to evaluate existing estimates of alcohol problems in the Danish population. The findings regarding alcohol dependence were similar to prior estimates; however, adjustment for nonparticipation indicated that previous figures have underestimated heavy drinking and harmful alcohol use in the Danish population by approximately 300,000 and 430,000 persons, respectively (111). Unfortunately, though, at the time of the PhD project design in 2018, the list of 2011 survey non-responders was no longer available. Thus, it must be acknowledged that there is a small risk that selection bias could have affected the findings from Study 2 and Study 3.

Study 1

Selection bias can also be a concern for systematic reviews, such as scoping reviews, wherein the included studies are not representative of the target population of studies. As the studies included in Study 1 were limited to English language publications, it is possible that this type of language bias could have affected the findings (310). However, investigations of the effect of restricting reviews to English-language publications have not found that this leads to systematic bias or significantly alters the findings (317, 318). As well, it is possible that the search strategy employed in Study 1 excluded certain relevant members of the target population. As mentioned by Laslett and Room in their published response to Study 1, "broadening the search scope beyond "records linkage" or variations on "register" (Supplement, Box 1) to add more specific descriptors of each system would have been a Sisyphean task but may be needed for a more complete inventory of studies based on records linkage" (319). For instance, specific registers may be mentioned by name, although the term "register" does not appear in the title, or other terms may be used (e.g., "claims administrative data") (319). However, broadening the search terms in this way would likely involve privileging "recall (completeness of retrieval)" at the expense of "precision (purity of retrieval)" (320) and would likely identify other administrative sources, such as private insurance databases, which, while interesting, are in a different category than the "centralized registers" addressed by Study 1. For instance, private insurance databases, such as those in the United States, have very particular selection criteria and, for instance, individuals may age-out (as when they become ineligible under their parents' insurance). As well, because the search terms prioritized household relations, the review may not have identified all studies of extended family members.

Study 1's focus on family relationships meant that register-based research on other areas of alcohol's harms to others had not been reviewed. Given the nature of the data, aside from perhaps studies of drink-driving injuries and deaths, register studies may be unable to identify the kinds of harms that could afflict strangers, such as being disturbed by noisy partygoers or feeling unsafe when encountering intoxicated strangers on the street. But since register studies can easily identify relatives and link records via a personal identification number, they are a fruitful source of information for alcohol's harms to family members, and, thus, families were the focus of Study 1.

Concerns regarding the sampling frame also apply to systematic reviews due to, for instance, publication bias. Publication bias refers to the fact that the published studies are not representative of the full body of work undertaken on a research question, with, for example, statistically significant findings more likely to be published (310). The risk of this type of bias may have been decreased (but not eliminated) had Study 1 included grey literature.

Information bias and misclassification

Information bias refers to systematic errors in data collection (310, 321). Relatedly, misclassification occurs in a study when a participant's exposure or disease status is categorized incorrectly. Misclassification can either be differential or non-differential, with the former referring to misclassification that is the same for study groups (e.g., outcome misclassification is the same for exposed and unexposed group) and the latter referring to misclassification (e.g., errors in categorizing outcome status, such as, diseased or non-diseased) that differ depending on exposure status (321).

Alcohol exposure in Study 2 and Study 3

The studies used self-reported information on alcohol consumption (Study 2 and Study 3) and alcohol-related problems (Study 3) to categorize participants. As discussed in the Introduction of this thesis, prior studies have questioned the accuracy of self-reported alcohol indicators, with survey measures tending to underestimate consumption (15, 110, 120). Various explanations for inaccuracies in self-reports include respondents' difficulties remembering the frequency and quantity of consumption, especially when they are asked to recall this information over a long period, and social desirability bias (15, 19), meaning that, due to the stigma associated with alcohol problems and heavy drinking, a respondent may underreport consumption or alcohol problems to avoid being perceived negatively (322).

AUDIT consumption questions (questions 1-3) can be characterized as self-reported measures of "customary or usual drinking habits" (15, 323) and require the respondent to estimate how frequently and how much they drink, on average. This contrasts with methods in which participants report detailed information on particular drinking occasions over a short period, and then, based on this information, average drinking behaviors are calculated by the researcher. Although "customary or usual drinking habits" questions have their advantages, including accounting for seasonal variations and including a long-enough reference period to more accurately estimate abstainers, respondents may forget drinking occasions, resulting in figures that underestimate true average drinking behaviors (15, 324). However, by

incorporating information from beverage-specific questions, Study 2 and Study 3 likely reduced underreporting as more detailed questions tend to result in higher consumption figures (14, 298, 299). Other features of the survey helped to reduce measurement error, including specific instructions and examples for the respondent on what defines "a drink".

Another potential concern is that exposure status was based on a single measurement point - in autumn 2011 - while participants were followed in the study until then end of 2018. Previous longitudinal AUDIT validation studies have also relied on a single (baseline) AUDIT measure (281). There is evidence both of stability and variation in drinking behaviors over time, depending on follow-up time, age, and baseline drinking status, with more individual variation among heavy drinkers (325, 326). Thus, we cannot be sure if participants' exposure status remained consistent during the study period, or, possibly, represented a peak or a low point in consumption. In terms of alcohol habits over the lifetime, some studies show that typical drinking trajectories involve consumption that peaks in adolescence and early adulthood, decreases and stabilizes in mid adulthood, and decreases during late adulthood (327). It should also be mentioned that while exposure was assessed only once, the measure is an indicator of usual drinking behaviors over the past year and not behavior on a particular day. However, even if there was some variability in alcohol consumption and problems during the study period, it is not obvious that changes would have been sufficient to move participants above or below the AUDIT/AUDIT-C cutoffs used. Further, any misclassification that did occur due to life-stage changes over the study period would be in both directions given that participants were of varying ages, with some participants increasing their consumption and possibly moving above the cutoff and some decreasing their drinking and possibly moving below the cutoff. Had the project been able to include repeated measurements, changes in drinking behaviors could have been assessed, and perhaps, alcohol exposure could have been treated as time-varying in the analyses (328).

There may also have been some misclassification resulting from AUDIT/AUDIT-C cutoff points chosen in Study 2 and Study 3. Prior studies have demonstrated that optimal AUDIT/AUDIT-C cutoffs might be slightly higher or lower in different countries (73, 329) and in specific subpopulations (74, 330, 331). For instance, some studies have shown that the optimal AUDIT and AUDIT-C cut-points are lower for women than men (174, 332) and even that the definition of binge drinking used in the AUDIT (in terms of number of drinks consumed) should be gender adjusted (333). The use of gender-adjusted alcohol measures, screening tools, and government-issued "low-risk" and "high-risk" alcohol guidelines is

rooted in the body of research showing that women have higher blood ethanol levels than men after consuming the same amount of alcohol, which may owe to differences in body mass, body water content, and metabolism of alcohol, and, that, as a result, women may experience alcohol-related health harms and impaired cognitive and motor performance at lower alcohol levels (334). However, there are also reasons why gender-adjustment may not be advised, such as if there are other drinking behaviors (such as the pace at which alcohol is consumed) and subjective experiences, which offset the biological differences in the effects of quantity of alcohol consumed (335). An evaluation of the ability of gender-variant and gender-invariant low-risk drinking guidelines to predict harm found that both performed well, with slight differences depending on the type of harm assessed (336).

Overall, there is a lack of consensus among alcohol researchers on whether gender differences in response to alcohol should translate into different cutoffs for alcohol consumption measures, and relatedly, cutoff scores for screening tools like the AUDIT and AUDIT-C. The cutoff points used in this thesis were selected because they are widely used or have already been established in a similar population. Assessing the validity of the AUDIT/AUDIT-C using these commonly applied cutoffs is an important task for alcohol research. While it is acknowledged that the optimal cutoff for the population consisting of 2011 Danish National Alcohol and Drug Survey respondents may have been slightly different, there is also a significant advantage to maintaining consistency in AUDIT/AUDIT-C studies if the findings are to have practical applications and the tools are to be used in a clinical context. For example, in a busy general practice or emergency department setting, established guidelines regarding cutoffs must be simple and as consistent as possible if the screening tools are to be used by staff. Sensitivity analysis in Study 3 using alternate cutpoints derived from ROC analysis yielded similar results to the main analysis, indicating misclassification due to the selection of cutoff points was unlikely to have biased the results. However, in the future, further sensitivity analyses could be undertaken to assess the impact of using gender-specific cutoffs as regards the association between AUDIT/AUDIT-C and the outcomes investigated by Study 2 and Study 3.

If misclassification of exposure occurred for any of the above reasons, it would most likely be non-differential, since alcohol exposure data were recorded prior to the recording of outcome data on hospitalization. Thus, the effect of such misclassification would have biased the effect toward the null. However, there is some risk of differential misclassification of alcohol exposure in Study 3 if participants with early-stage ARDD (but who had not yet been

hospitalized for the conditions) systematically misreported consumption. There is some prior research that shows that misreporting is associated with drinking-risk status, but it is not clear whether it is low- or high-risk drinkers who are more likely to underreport consumption (e.g., (337, 338)).

Outcomes in Study 2 and Study 3

There is also the possibility that there was some misclassification of the outcomes of violence victimization (Study 2) identified by the "reason for contact" code (i.e., act of violence) and ARDD (Study 3) identified by ICD diagnosis codes in the national patient register. First, I will discuss the potential for misclassification of hospitalizations for these conditions.

There have been prior validations studies of individual variables included in the Danish National Patient Register, with results indicating that data quality varies widely (132). As regards the specific variables relevant for this thesis, however, there have been few validation studies of the "reason for contact" codes after the inclusion of emergency room and outpatient data in the register. Kruse et al. (306) compared physical assaults reported to police (as registered in the Victims Statistics) with hospital admissions with a reason-for-contact code of violence in the National Patient Register. A "high degree of overlap" was noted, with 32% of registrations in the National Patient Register in 2006 also appearing in the Victims Statistics (306), which would indicate a low false positive rate. However, there may have been hospital admissions in Study 2 that were misclassified, and, if so, these would most likely be admissions related to acts of violence that failed to receive a reason for contact code of violence (false negatives) because hospital staff lacked the relevant information. For instance, injuries may not have been obviously violence-related or the patient (possible due to social desirability bias) or ambulance staff may not have reported that the injuries were caused by violence. Such misclassification may have been differential, if, for instance, staff were more likely to record a reason for contact code of violence if a patient was obviously intoxicated at the time of the admission, but failed to record the admission as caused by violence for a patient who presented in otherwise the same condition. Alternatively, a victimized individual who was intoxicated may be unable to provide staff with sufficient information, while an individual who was not intoxicated may have been able to give enough information for a violence reason for contact to be recorded. However, it is expected that emergency room staff are well positioned to identify violence-related injuries, as Danish

national strategies on violence have recommended and implemented training and awareness of staff who come in contact with victims of violence, including education of medical students in how to identify signs of intimate partner violence and the provision of informational materials to health professionals (e.g., the pamphlet "Violence in close relationships") (339-341).

As regards the accuracy of the outcome in Study 3 (ARDD diagnoses in hospital register) a study carried out using data on Danish psychiatric in-patients found significant underdiagnosing of substance use disorders in the Danish Psychiatric Register when compared to F1X diagnoses made using a diagnostic interview or from information in the medical records, with less under-diagnosing of alcohol use disorders compared to drug use disorders (342). Similar results have been found in the United States, where studies have shown that a substantial proportion of hospital patients who meet the criteria for an alcohol use disorders are not identified (343, 344). It should also be considered that alcohol use disorder diagnoses (i.e., made via ICD-10 criteria) are based on assessments of harm which may not be culturally invariant, for instance as regards concepts such as "impairment of control" and use of time/prioritization of time (345, 346).

Also relevant is a National Patient Register validation study of alcoholic liver cirrhosis diagnosis indicating a positive predictive value of 78% (95% CI: 74%–81%) (347). However, other than these, there appear to be no additional validation studies covering the other ARDD diagnosis codes included in Study 3. As noted by Babor et al. (42) in reference to ARDD, the "causal attribution built into these categories is substantially influenced by social factors." Thus, social factors effect whether or not an ARDD diagnosis is given, as opposed to, for instance, diseases of the digestive system without an alcohol specification. As mentioned in the Introduction, it is likely, due to stigma, there is under-diagnosing of alcohol-attributable conditions (43, 44), perhaps particularly among sociodemographic groups where alcohol problems are less expected (20). Ideally, prior to initiating a register-based study, a validity assessment of the relevant variables should be carried out. However, due to time and resource restrictions, this was not a feasible component of the thesis.

In addition to the potential for diagnostic errors discussed above, there may also have been administrative errors, which, as mentioned in the Introduction of this thesis, concern data entry errors when the information about the admission is transferred to the register (e.g., dates of admission, diagnosis, and reason for contact codes) (154). Such errors, if they

occurred, would be non-differential. As well, Study 3 excluded participants with a prior ARDD diagnosis because the aim was to assess incident cases; however, if a hospitalization occurred prior to the establishment of the National Patient Register, or prior to the adoption of the ICD-10, it was not detected, and, thus, some individuals may have been erroneously included in Study 3.

The above discussed has concerned hospitalizations for violence and ARDD, as these were how the outcomes were operationalized. However, if the overall categories of violence victimization and ARDD are considered, there may also be concerns about misclassification. As mentioned in the Introduction, registers tend to capture only the "tip of the iceberg". Thus, Study 2 likely missed a substantial portion of the instances of violence victimization experienced by respondents because the patient registers only captured the most serious violence-related injuries (306); some participants, may have received treatment for violencerelated injuries from general practitioners, for instance, and many more received no medical treatment at all. A 2010 review of literature on help-seeking behavior among victims of crime found "only a small fraction" of violent crime victims sought help from formal sources, such as the police, healthcare system, or social services (348). Formal sources can be defined as "professionals who have a legitimate and recognized professional role in providing relevant advice, support, and/or treatment" (349) (p. 175). These can be contrasted with informal sources, such as family and friends, which are distinguished by a "personal and not a professional relationship with the help-seeker" (349) (p. 175), and are more frequently sought out by victims of violent crime (348), but would not be recorded in a register. The behavioral model of health services use developed by Andersen and colleagues (350) has been proposed as a framework for understanding the likelihood of help-seeking and use of health services among victims of violence (348, 349, 351, 352). The model holds that three categories of variables are relevant for predicting healthcare use: predisposing characteristics (e.g., sociodemographics, health beliefs), enabling resources (i.e., factors that affect access, such as health insurance, income, transportation, travel time), and level of need (e.g., symptoms and severity of injury based on perception or an evaluation) (350) (353). Bearing in mind Mäkelä et al.'s (20) point that register data are not direct measures of variables but, rather, are measures of "service use", and the multitude of factors that likely influence whether a person utilizes healthcare put forward by the behavioral model, it is worth considering the limitations of using hospital registers, which capture only some of the instances of violent victimization.

Likewise, Study 3 only included the "tip of the iceberg" in terms of alcohol-related health problems among the general population sample since there are a large number of conditions that are partially attributable to drinking (44) and some may not be severe enough to lead to hospitalization. As well, respondents with certain types of ARDD, such as alcohol use disorders, may have received treatment elsewhere, such as non-hospital-based public and private alcohol treatment institutions, or may not have received any treatment, although barriers to receiving treatment are likely lower in Denmark than other countries such as the United States, since individuals can receive free treatment from the health system (197). WHO estimates indicated a 12-month alcohol use disorder prevalence of 7.5% among Danish adults 15 years and older as of 2016 (1), which is a significantly higher figure than would be indicated by the hospital data from Study 3. Additional ARDD may have been identified had the Danish National Alcohol Treatment Register been included in the study. Thus, the conclusions from Study 2 and Study 3 apply to serious, hospital-related outcomes.

Although not the main focus of the analyses, Study 3 showed that individuals with prior psychiatric illness, as indicated by a hospital-based diagnosis before baseline, had a higher risk for ARDD, even in the multivariable model that controlled for AUDIT-C/AUDIT score. It could be that such individuals are more likely to be classified as having an ARDD because they are already in the hospital treatment setting due to their pre-existing mental disorder. As well, hospital staff may be more likely to assess for ARDD if a patient has a comorbid psychiatric condition, making an ARDD more likely to be identified and recorded among these individuals. As well, individuals with comorbid alcohol use disorder and other psychiatric conditions may be more likely to receive hospital treatment than individuals without comorbidity – again making a registration in the hospital register more likely (197).

Study 1

There may have been a form of misclassification in Study 1, wherein studies were erroneously included or excluded in the review or where errors were made in the data charting. Since Study 1 aimed to map the range of research, liberal criteria for including outcomes were applied. Thus, while an argument could be made that outcomes such as an increased risk of conviction among children of heavy drinkers might better reflect the children causing harm than experiencing harm, such outcomes were included, since involvement with the criminal justice system is associated with various adverse outcomes for the individual (354). Similarly, while foster care placement could represent a response to managing harm from a heavy-drinking family member, it is also likely a proxy for

maltreatment and neglect within the family, and children in out-of-home care have a higher risk of exposure to a range of other adverse childhood experiences (355).

One author of Study 1 screened the titles and abstracts of the articles identified from the search and carried out the majority of the full-text review and the data charting. Including multiple authors in this process may have minimized classification errors (161).

Common methods bias

Combining survey-based measures of alcohol exposure and register-based outcomes, as was done in both Study 2 and Study 3, also had the advantage of reducing bias due to common methods variance (356). This is because the observed covariation between exposure and outcome does not arise from the same method being used to measure both variables. In studies in which only self-report measures are used, on the other hand, common methods bias can derive from common rater effects such as consistency motif and social desirability (356, 357). Covariation in such studies may be attributed to respondents' tendency to attempt to answer consistently or provide responses that are socially acceptable (356, 357). Since Study 2 and Study 3 used an outcome variable that was not based on self-report, it can be ruled out that the observed associations between AUDIT/AUDIT-C scores and hospitalizations are due to the use of common methods.

Confounding

As mentioned in the Introduction, one weakness of registers is that information prior to the establishment of the registers is not available to researchers. Both Study 2 and Study 3 controlled for prior psychiatric diagnoses in the analysis. However, diagnoses that occurred prior to the creation of the National Patient Register or prior to the use of the ICD-10, as well as mental health problems that did not result in a hospital contact, were not identified and accounted for in the analyses, and thus may have resulted in some residual confounding.

There may have also been confounding due to unmeasured confounders. In Study 2, other than the acute effects of intoxication, there may be other possible explanations for the increased rate of violence hospitalization among respondents with hazardous drinking found in Study 2. For instance, heavy drinkers may spend more time around other heavy drinkers, who are themselves at higher risk for aggression and perpetrating violence (358) and in places like bars and pubs, which are settings that have been associated with an increased risk for violence (359). Criminal activity may have been an additional unmeasured factor, which

could have confounded the observed relationship. Adding information on the setting where the episode of violence occurred (50), the "wetness of the social environment" (360), and criminal history would have been helpful. As well, there may be individual characteristics of the respondents, such as poor impulse control, that could have acted as confounders.

Timing of measurements

The previously-discussed use of a single alcohol exposure measurement point as a longterm risk factor may have different implications for the interpretation of the results in Study 2 and Study 3. As mentioned earlier, a likely explanation for the association between alcohol and violence victimization is the physiological effects of intoxication, and, therefore, an association between a high AUDIT score in 2011 and hospitalization for violence during the follow-up period implies that the hazardous consumption measured at baseline continued during the follow-up and also occurred proximally to the outcome.

While the alcohol-violence victimization relationship may be due to the effects of acute intoxication, for most ARDD, however, the outcome likely reflects a cumulative effect of heavy alcohol consumption over a sustained period, and a long follow-up is therefore required for the condition to develop. The association between a high AUDIT score and ARDD hospital admission does imply that, in most cases, the hazardous alcohol consumption indicated by the AUDIT persisted for an extended period. However, it does not necessarily imply heavy alcohol use at the time of the hospitalization since some individuals may reduce or eliminate their alcohol consumption because they are feeling ill or because they are trying to address prior problematic alcohol use in the period immediately preceding their diagnosis, and not all ARDD may be reversed in response to abstention or a reduction in alcohol consumption (361).

Sensitivity analyses using a shorter follow-up periods could have been useful in Study 2 and Study 3; however, given the rarity of the outcomes, a larger sample would have likely been required. Future studies could investigate this matter, while first performing a power analysis to identify the number of participants needed – a step which was not carried out as part of the thesis. As these types of studies involve censoring, such a power analysis would need to include an estimation of the number of subjects expected to experience the event (i.e., not censored) at the specified follow-up time (362).

Internal and external validity

Internal validity refers to whether the observed results of the study are accurate and cannot be attributed to the effects of bias, confounding, or random error (47). Rothman et al. distinguish validity from precision with the former influenced by bias and the latter by random error (46).

As discussed in the prior sections, it cannot be ruled out that the results of Study 2 and Study 3 were impacted by bias and confounding. However, confounding was addressed by adjusting for relevant variables in the analyses, and methodological features of the studies likely minimized the magnitude of bias. For instance, the use of random sampling, a relatively high response rate and a high follow-up rate, and the use of weighting in the analyses make it unlikely that selection bias had a large impact on the findings of Study 2 and Study 3. Information bias and misclassification were minimized by the use of beveragespecific questions to assess alcohol exposure, and, sensitivity analysis in Study 3 using alternate cutoffs for the AUDIT, supported the original analysis. As well, there does not appear to be a substantial risk of bias in Study 1. Thus, on the whole, the studies are judged to have internal validity.

External validity presupposes internal validity, and refers to whether the results of the study can be generalized to those outside of the study population (47). The results of Study 2 and Study 3 are likely generalizable to general populations in countries with, for instance, similar sociodemographic profiles, healthcare systems, and drinking patterns (including gender-specific patterns) to Denmark.

CONCLUSIONS

Surveys and registers can be viewed as complementary sources of data in alcohol research (20, 319). Because they may capture different populations and are uniquely suited to assess different aspects and levels of alcohol exposure and outcomes, findings from register and survey studies can be compared and contrasted in order to clarify and specify the relationship between alcohol and harms to the drinker and others. For instance, whereas surveys are apt for measuring outcomes that are common, less serious, or less tangible, registers are better able to measure outcomes that are long-term, rare, or severe. However, beyond being complementary, the relationship between these sources could be characterized

as compensatory in the sense that many of the limitations of the one source are counterbalanced by the strengths of the other.

By considering findings from these very different data sources, evidence of relationships between alcohol and harm can be strengthened, inconsistencies can be identified, and new insights can be gained. This thesis addressed the triangulation of data and, beyond this, also demonstrated ways that survey and register data can be linked within the same study to provide richer understandings of topics relevant in research on alcohol-related harms. For instance, Study 2 identified an effect of gender on the relationship between hazardous drinking in the general population and severe violence victimization, and Study 3 included the full range of ARDD in an AUDIT validity study among members of the general population.

Laslett and Room (319) remarked that Study 1 "points toward a wider scope in which register data sets can contribute to documenting, investigating, and prevention planning for harms from others' drinking. (p. 458). As illustrated by Study 2 and Study 3, the same could be said about harms to the drinker.

The work in these studies could be extended. For instance, additional instances of interpersonal violence could be identified in the registers using ICD-10 codes (i.e., a head or neck lesion) and location of incident (i.e., residential area), indicators which are both available in the Danish National Patient Register (258). As well, survey data could be merged with additional Danish registers, such as the Victims Statistics, to identify violence victimization that did not result in hospitalization (306). As regards primary care contacts, diagnostic information which would have been necessary to identify instances of ARDD and violence victimization were not available in the Danish registers during the period covered by the studies (140). However, this type of information is available in other Nordic countries (140), and could be incorporated into future studies. For instance, in Finland, International Classification of Primary Care (ICPC) codes are used to classify, for example, presenting problems and diagnoses related to healthcare visits to general practice (20).

Similar hospital-based register information is available in all Nordic countries. Based on geography, drinking patterns, and economic factors, the Nordic countries are frequently grouped together (9, 363), although some researchers point to differences in terms of level of alcohol consumption, beverage preferences, intoxication culture, and alcohol policy (7, 9, 363-365). Thus, comparative studies based on Study 2 and Study 3, using survey and hospital

register data from multiple countries, would be interesting to assess similarities and differences in the Nordic countries.

Naimi et al. have demonstrated that more restrictive alcohol policy environments (measured by a composite indicator) are associated with lower odds of alcohol-related homicide victimization (366). Comparative studies could use hospital register data to assess whether the alcohol policy environment is associated with violence-related hospitalization.

Future studies could also involve validations of additional indicators in the National Patient Register, such as the reason for contact codes and the full range of ARDD. Having such additional background information on the quality of these indicators is important for assessing their overall usefulness for research purposes.

This thesis has implications for alcohol-related research methods and the design of future studies of alcohol-related harm. Including long lists of questions, such as rare health consequences, runs the real risk of respondents experiencing "survey fatigue" and providing lower quality responses (367). Thus, depending on the research question, it may be prudent for researchers to only include AUDIT-C questions in general population surveys, rather than the full AUDIT.

The findings from this thesis may also have some clinical applications. Some previous studies have demonstrated the effectiveness of Screening, Brief Intervention, and Referral to Treatment (SBIRT), including when administered in an emergency room setting, in reducing alcohol consumption, injuries, and emergency room visits (368-371). In terms of clinical relevance, if the recorded violence-related hospital admissions can be understood as the "tip of the iceberg", findings from Study 2 may offer some tentative, preliminary support for targeting brief emergency-room based interventions in Denmark to males.

Another related application of the thesis concerns the screening tools used in SBIRT. SBIRT have been identified as an effective intervention to reduce alcohol consumption and related harm (372, 373). However, it is estimated that a low proportion of the individuals with hazardous and harmful alcohol use are screened and receive a brief intervention and that a similarly low proportion with alcohol dependence have been in contact with treatment specialists (373). A necessary first step of SBIRT is to use a screening tool, such as the AUDIT or AUDIT-C, to identify those who should receive brief advice and referral to treatment. Given that one of the identified barriers to the implementation of SBIRT is a perceived lack of time (374), the results of Study 3 offer some support for using the brief

AUDIT-C as a screening tool. This does not necessarily imply that it would be an efficient use of time to screen members of the general population for risk of hospitalization for ARDD, which although likely under-recorded in the register, remains a rare outcome. However, if, as argued previously, ARDD represent merely a small portion of the alcohol-attributable conditions, with partially alcohol-attributable conditions constituting the bulk, screenings using the AUDIT-C could identify many more people at risk for alcohol-attributable conditions (1).

A further takeaway from the thesis concerns potential modifications that could be made to the register-based healthcare indicators of violence. Researchers and international organizations have advocated for the recording of specific information that could improve the accuracy of violence-related statistics, especially among women (375). This includes the recording of the relationship between the victim and the perpetrator when victims are seen in medical settings (375, 376). There are ICD-10 codes that specify the perpetrator (i.e., Y07 Perpetrator of assault, maltreatment and neglect), though these are not used in the Danish National Patient Register (306). Information on the victim-perpetrator relationship may already be in the narrative records in the patient file, even though it is not coded and entered in the register (375). Including such additional indicators in the National Patient Register could help to illuminate gender differences and identify instances of intimate partner violence.

Surveys have been the workhorse of alcohol research. However, the general decline in survey response rates (119, 377), which has not spared alcohol research specifically (378, 379), means that researchers may increasingly need to look towards other data sources. While surveys have been, and will likely continue to be, a crucial data source in alcohol research, "mining" register data will allow researchers to remedy problems associated with low survey response rates and to explore areas less accessible by survey methods. Given the long history of registers, unique person identification numbers, and dominance of the publicly funded healthcare system in the Nordic region, researchers in these countries are in an enviable position to exploit this rich data source.

ENGLISH SUMMARY

Globally, among people aged 25–49 years, alcohol use is the leading risk factor for morbidity and mortality when assessed by using disability-adjusted life years (380). In addition to health harms, heavy drinking has been associated with adverse social consequences for the drinker and others (34, 381). Assessing relationships between alcohol use and various harms requires data sources that accurately measure both hazardous drinking and outcomes. Surveys have advantages over other data sources in providing a high level of detail on volume and pattern of drinking, in capturing subclinical alcohol use, and in measuring non-tangible harms, such as fears. However, limitations, including non-response bias, underreporting of consumption and harms, and lack of separation of exposure and outcome in survey items, mean that a fuller understanding of the relationship between alcohol and harms requires supplementing survey data with other sources. Registers have many features that make them a suitable complement to survey data, including wide coverage over long periods and the ability to capture rare and serious indicators of alcohol exposure and harm. Register data can also be used to verify survey data in terms of whether information from self-reports translates into registered outcomes. The aims of this thesis were to examine how register data contribute to an understanding of alcohol's harms to family members (Study 1), and to investigate whether hazardous drinking as reported by respondents of a national survey is associated with subsequent hospitalizations for violence (Study 2) and alcohol-related disorders and diseases (ARDD) (Study 3) recorded in a patient register.

The first study was a scoping review that mapped the existing research literature on register-based studies of alcohol's harms to family members. Database and reference list searches identified 5,961 unique records eligible for screening, and 91 of these met the inclusion criteria. The majority of included studies drew on hospital registers to identify heavy drinkers and focused on the parent-child relationship. The review demonstrated that the register-based methodology allows for assessment of a range of serious and precisely defined outcomes over the short- and long-term, which affect children of very heavy drinkers. Register-based studies have shown that parental heavy drinking is associated with an elevated risk of offspring hospitalizations for specific diseases and disorders, mortality, criminality, poor employment and educational outcomes, abuse/neglect, and placement in residential/foster care.

The second study was a historical cohort study in which the study population consisted of respondents to the 2011 Danish National Survey on Alcohol and Drugs (N=5,126), who were followed in the Danish National Patient Register from 2010–2018. The study investigated the association between hazardous drinking and subsequent hospital admissions for violence using a Poisson regression model. Adjusted analyses showed that general population respondents with self-reported hazardous drinking (AUDIT-C \geq 5 points) had an increased rate of subsequent hospital admissions for violence (incidence rate ratio (IRR) = 2.28, 95% confidence interval (CI)=1.16–4.50) compared to respondents without hazardous alcohol use (AUDIT-C < 5 points) and that increasing AUDIT-C scores were associated with an increasing rate of violence-related admissions (IRR=1.20, 95% CI=1.06–1.37). Gender was found to moderate the effect of increasing AUDIT-C score on hospital admissions for violence (IRR=0.69, 95% CI=0.53–0.90).

In the third study, the 2011 survey respondent cohort (N=4,522) was followed using Danish national registers to hospitalization for incident ARDD, emigration, death, or December 31, 2018, whichever occurred first. During follow-up, 56 respondents had an incident ARDD admission. Cox regression analysis showed that respondents with high AUDIT (\geq 8 points) and AUDIT-C (\geq 5 points) scores had a significantly increased risk of an ARDD hospital admission (AUDIT: hazard ratio (HR)=4.72, 95% CI=2.59-8.60; AUDIT-C: HR=7.97, 95% CI=3.66-17.31) compared to respondents who scored below these cutoffs. This study offers further support for the validity of the AUDIT and AUDIT-C, showing that scores above the cutoffs in both instruments are associated with severe, long-term alcoholrelated health outcomes.

The studies that make up this thesis demonstrated the complementary and compensatory roles of survey and register data in alcohol research. The thesis showed how comparing findings from survey- and register-based studies, as well as linking survey and register data in the same study, can further our understanding of the relationship between alcohol use and harm to the drinker and to others.

DANSK RESUMÉ

Globalt set er alkoholindtag blandt 25-49-årige den primære risikofaktor for sygdom og morbiditet, når man evaluerer ved at bruge sygdomsjusterede leveår (380). Udover helbredsskader er et stort alkoholforbrug associeret med negative sociale konsekvenser for både den, som drikker og andre (34, 381). For at undersøge forholdet mellem alkoholindtag og forskellige skadevirkninger kræves der datakilder, som præcist måler både alkoholforbrug og skadevirkninger. Spørgeskemaundersøgelser har fordele overfor andre datakilder da de kan give en meget detaljeret information om både mængden og mønsteret for alkoholindtag, da de kan indfange ikke-klinisk risikabelt alkoholindtag, og da de kan indikere mindre håndgribelige skadevirkninger, såsom frygt. På den anden side har spørgeskemaundersøgelser begrænsninger såsom non-response bias, underrapportering af alkoholforbrug og skadevirkninger, samt mangel på adskillelse mellem alkoholforbruget og dets effekter. Disse begrænsninger betyder, at spørgeskemadata bør suppleres med andre typer af datakilder for at få en mere omfattende forståelse af forholdet mellem alkohol og skadevirkninger. Registre har mange egenskaber, som gør dem passende til at levere supplerende data. Disse egenskaber inkluderer en bred vifte af informationer over længere perioder samt potentialet for at indfange sjældne og væsentlige indikatorer for alkoholindtag og skadevirkninger. Registerdata kan også bruges til at verificere spørgeskemaundersøgelsesdata med henblik på at afgøre, hvorvidt information fra selvrapportering korrelerer med observerede udfald. Afhandlingens tre delmål var at undersøge, hvorledes register data kan bidrage i undersøgelser af alkohols skadelige virkninger overfor familiemedlemmer (Studie 1), og at undersøge hvorvidt et risikabelt alkoholforbrug, som er rapporteret i en spørgeskemaundersøgelse, er associeret med efterfølgende hospitalskontakter i forbindelse med vold (Studie 2) samt alkohol relaterede psykiske lidelser og sygdomme (ARDD) registeret i Landspatientregisteret (Studie 3).

Det første studie var et *scoping review*, som kortlagde den eksisterende forskningslitteratur om registerbaserede studier af alkohols skadevirkninger for familiemedlemmer. Via databaser og litteraturlister blev 5961 unikke potentielle studier identificeret, og af disse mødte 91 inklusionskriterierne. Majoriteten af de inkluderede undersøgelser brugte hospitalsregistre til at identificere alkoholbrugere med et stort forbrug og fokuserede på forældre-barn relationer. *Scoping reviewet* viste, at registerbaseret metodologi kan bidrage til forståelsen af en række væsentlige og præcist definerede udfald, som over kortere eller længere tid påvirker børn af forældre med et stort alkoholforbrug. Registerbaserede studier viser stærk evidens for, at forældres alkoholindtag betyder en øget risiko for børnene i form af indlæggelser for specifikke sygdomme og lidelser, højere dødelighed, kriminalitet, arbejdsløshed og uddannelsespræstation, misbrug og forsømmelse, og anbringelse i familiepleje eller institutionel pleje.

Det andet studie var et historisk kohortestudie af en population, som bestod af respondenter fra "Dansk National Undersøgelse af Alkohol og Stoffer" gennemført i 2011 (N=5126), og som blev koblet med data fra det nationale danske patientregister fra 2010-2018. Undersøgelsen angik forholdet mellem risikabelt alkoholindtag og efterfølgende hospitalsindlæggelse for vold ved at benytte en Poisson regressionsmodel. Justerede analyser påviste, at respondenter med et selv-rapporterede risikabelt alkoholindtag (AUDIT-C \geq 5 points), havde et øget ratio af efterfølgende hospitalsindlæggelser for vold (incidensrate ratio (IRR) = 2.28, 95% konfidensinterval (KI)=1.16–4.50). Studiet viste endvidere, at køn modererede effekten ved at øge AUDIT-C indikatoren for hospitalsindlæggelser for vold (IRR=0.69, 95% KI=0.53–0.90).

I det tredje studie blev undersøgelsens kohorte (N=4522) fulgt fra 2011 ved at benytte danske national registres data for hospitalsindlæggelse for ARDD, emigration, død, eller 31. december 2018 afhængigt af, hvad der indtraf først. I løbet af denne periode havde 56 respondenter en ARDD indlæggelse. En Cox regression analyse viste, at respondenter med høj AUDIT (\geq 8 points) og AUDIT-C (\geq 5 points) score havde en signifikant øget risiko for en ARDD hospitalsindlæggelse (AUDIT: *hazard ratio* (HR)=4.72, 95% KI=2.59-8.60; AUDIT-C: HR=7.97, 95% KI=3.66-17.31) sammenlignet med respondenter, som scorede under disse grænser. Dette studie giver yderligere evidens for validiteten af AUDIT og AUDIT-C screeningsinstrumenter ved at vise, at scorer over grænserne i begge screeningsinstrumenter er associeret med en svær grad af længerevarende alkoholrelaterede sundhedsproblemer.

Studierne, som udgør denne afhandling, demonstrerede, hvorledes data fra henholdsvis spørgeskemaundersøgelser og registre kan komplementere og kompensere for hinanden i alkoholforskning. Afhandlingen viste, hvordan sammenligning af observationer fra spørgeskemaundersøgelser og registerbaserede studier, såvel som sammenkædning af spørgeskemadata og registerdata i det samme studie, kan bidrage til forståelsen af sammenhængen mellem alkoholbrug og skadevirkninger til alkoholbrugeren og andre.

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APPENDIX

Manuscripts of individual studies

- Study 1 Brummer, J., Hesse, M., Frederiksen, K. S., Karriker-Jaffe, K. J., & Bloomfield, K. (2021). How do register-based studies contribute to our understanding of alcohol's harms to family members? A scoping review of relevant literature. *Journal of Studies on Alcohol and Drugs*, 82(4), 445–456.
- Study 2 Brummer, J., Bloomfield, K., Karriker-Jaffe, K. J., & Hesse, M. (2022).
 Hazardous drinking and violence-related hospitalizations in the Danish general population: A historical cohort study. *Drug and Alcohol Dependence*, 233, 109338.
- Study 3 Brummer, J., Bloomfield, K., Karriker-Jaffe, K. J., Pedersen, M.M. & Hesse, M. (2023). Using the Alcohol Use Disorders Identification Test to predict admission for alcohol-related conditions in the Danish general population: A record-linkage study. *Addiction (Abingdon, England)*, 118(1), 86–94.

How Do Register-Based Studies Contribute to Our Understanding of Alcohol's Harms to Family Members? A Scoping Review of Relevant Literature

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ABSTRACT. Objective: This review maps the research literature on register-based studies of alcohol's harms to family members and identifies areas for future research. **Method:** Using a scoping review methodology, the PubMed/MEDLINE, EMBASE, and PsycINFO databases were searched in August 2019 with keywords to identify studies that included register-based outcome sources, a family relationship, and an exposure to heavy drinking. In total, 5,961 records were screened, 403 full-text articles were assessed for eligibility, and 91 studies were included in the final review. **Results:** Register-based research on alcohol's harms to family members has largely drawn on hospital records to identify heavy drinkers and has primarily focused on children of heavy drinkers; 79 of the included studies solely investigated harms to children, whereas 2 focused on partners and 10 on multiple first-degree or unspecified relatives. Register-based studies show that children of heavy

In WHAT WAYS does alcohol cause harm to others than those who drink themselves? Within the last 10 years, there has been an expansion of research on consequences that extend beyond the drinker, with alcohol's harm to others regarded as an umbrella term for a range of long- and shortterm effects, of varying degrees of severity, inflicted by both known persons and strangers, and at both the individual and societal levels (Laslett et al., 2019). Although some studies show that harm because of strangers' drinking may be more prevalent (Laslett et al., 2011), harms caused by close relations, such as household family members and friends, may be more severe (Laslett et al., 2011) and distressing (Karriker-Jaffe et al., 2017).

Survey data have been an important source of information about the magnitude of alcohol's harms to others (Rossow, 2015) and can measure outcomes not easily assessed by other means, such as fear of harm (e.g., feeling unsafe because of others' drinking). However, surveys often rely on self-reports of alcohol-related harms, which may be influenced by individual, cultural, or temporal factors (Room et al., 2016; Rossow, 2015). It could be problematic, then, if drinkers are at a higher risk for mental disorders, disease and injury hospitalizations, infant and child mortality, criminality, poor employment and educational outcomes, abuse/neglect, and placement in residential/ foster care, among other negative outcomes. **Conclusions:** A substantial body of register-based research shows that children of parents with the most severe alcohol problems are at an increased risk for numerous adverse experiences. Register-based studies have investigated diverse, yet precisely defined outcomes, using large samples followed over long periods, and have examined the contribution of genetic, biological, and environmental factors. Our understanding of alcohol's harms to families could be enhanced by further register-based research on other household family members of heavy drinkers. (*J. Stud. Alcohol Drugs, 82,* 445–456, 2021)

our understanding of alcohol's harms to others were based solely on surveys that ask participants to judge whether an undesirable event for oneself or others was attributable to alcohol. There is a need for some reflection on approaches to measure alcohol's harms to others and the sources of data used to describe and quantify these harms.

Some of the limitations of population surveys could be addressed by complementing such research with registerbased data (Lund & Bukten, 2015; Rossow, 2015). Until now, however, the contribution of register-based studies has not been adequately reviewed. Register-based studies analyze existing population registers consisting of individual-level data, which have been systematically collected and regularly updated on a complete target population (United Nations Economic Commission for Europe, 2007). Like surveys, register-based research has the advantage of large study populations, and registers' wide population coverage minimizes biases attributable to selection and attrition (Thygesen & Ersbøll, 2014). Furthermore, these data are often available over extended periods, thereby allowing assessment of longterm consequences. Thus, registers are apt for capturing a range of potential harms, including rare but severe outcomes in such areas as mental health and violence (Rossow, 2015).

Register-based studies can establish associations between alcohol and harm in numerous ways. This link may be made directly, such as when alcohol's role in an event is recorded in the same register entry as the assessed outcome. For in-

Received: June 30, 2020. Revision: January 29, 2021.

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stance, registers of child abuse or protection measures may also record parental heavy drinking. The link may also be made through statistical analyses showing an increased risk of harm (Rossow, 2015). Since register studies can identify relatives and link records via a personal identification number, they are a fruitful source of information for alcohol's harms to family members. Previous reviews have investigated outcomes for the family as a whole (Hutchinson et al., 2014) and for children specifically (Rossow et al., 2016; Staton-Tindall et al., 2013), but we are unaware of reviews that have explored the contribution of register-based research.

The aim of this current review is to map the literature on register-based studies of alcohol's harms to family members. Accordingly, the review addresses the following research questions:

- 1. Which family members, in terms of relationship to the drinker, are the focus of the studies?
- 2. How has the exposure been operationalized?
- 3. What harms/outcomes for family members of heavy drinkers have been investigated?
- 4. What are the main findings of register-based studies, and how do the findings differ from those of survey-based studies, if at all?
- 5. What are the gaps in existing register-based research on alcohol's harms to family members?

Method

Study design

We used the scoping review methodology, which, although similar to that of a systematic review, is guided by the unique objective of charting the available literature on a research topic (Pham et al., 2014). The process of identifying and presenting the literature is distinguished by broader coverage and handling of the subject (Pham et al., 2014). Scoping reviews have as their main objectives to broadly describe all available research on a broad topic and identify understudied aspects (Arksey & O'Malley, 2005). This contrasts with systematic reviews, which are more narrowly focused and often aim to summarize results of comparable studies on a highly specific topic (Munn et al., 2018). The scoping review methodology was appropriate for the current review, as it is best suited to providing an overview of the literature and identifying areas where research is lacking. This review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist (Tricco et al., 2018).

Information sources and search strategy

The review of records was carried out in August 2019, in which studies were identified by searching three electronic research literature databases (PubMed/MEDLINE, EMBASE, and PsycINFO), using subject headings and terms related to relationship to the drinker, exposure, and data source (Supplemental Box 1). A final source was the reference lists of all included records. Scoping reviews may include nontraditional information sources, also known as grey literature (Tricco et al., 2018). This review, however, included only peer-reviewed studies; this served to maintain consistency with other reviews on this topic and operated as a rough quality check of included studies.

Eligibility criteria

The following criteria were used:

- Studies must have investigated alcohol use as an exposure. No constraints were placed on the exposure data source. Studies that combined alcohol and illicit drug use into a category of "substance use" were included. There were several reasons for this decision. First, alcohol is more prevalent than any illicit drug and associated with a larger burden of illness globally (Peacock et al., 2018). This means that when a nonspecific substance use disorder is coded in a register, it is more likely to be an alcohol use disorder than any other substance. Second, people with severe alcohol problems may often have concurrent use of illicit drugs, making the distinction difficult to make, even if an attempt has been made in the original study (Staines et al., 2001).
- 2. The outcome variable must have been focused on harm to a family member of the drinker. Any familial relationship, immediate or extended, was accepted; however, the search terms reflect that household relations are prioritized given their intense and prolonged exposure.
- 3. The outcome must have been reported using a centralized register as the data source.
- 4. Only individual studies were included.
- 5. Studies published in English were included, with no restrictions on date of publication.
- Studies that only assessed prenatal exposure or perinatal outcomes were excluded, as were studies with only substance-related outcomes.

The database searches identified 5,134 records, and a review of the included records' reference lists identified an additional 2,737 records. Duplicates from the database searches and reference lists were removed using EndNote X8.2, leaving a total of 5,961 unique records. The titles and abstracts of all unique records were screened by the first author, and based on this initial review, 403 of the records were selected for a review of the full text. Of these, 91 studies were assessed as meeting the inclusion criteria for the scoping review. Figure 1 presents the PRISMA flowchart of the selection process.



FIGURE 1. Flow diagram of records screened, assessed, and included in the review. Note: Some articles were excluded for multiple reasons.

Data charting and extraction

The following descriptive characteristics were extracted from each record: author(s), publication year, title, study focus, study population, length of follow-up, exposure measure (including data source and definition of heavy drinking), relationship between the drinker and family member, outcome measures (including data source and definition), and main findings. "Exposure" refers to exposure to a heavy-drinking family member. We applied a broad definition of "heavy drinking" because we wanted to include a range of ways in which problematic use of alcohol was operationalized. The extracted data were grouped into overarching categories, and the number of studies that fell into each category was totaled and reported in tables. Some studies used multiple sources to define heavy drinking and/or included multiple outcome measures.

A vote-counting procedure, also known as a box-score method, was used to summarize the main findings of the subset of studies in which substance use of a family member was the primary explanatory variable. This procedure, chosen because of the heterogeneity of the studies, involved totaling the number of studies with significant positive, significant negative, and nonsignificant findings (Light & Smith, 1971). Substance use was defined as heavy drinking, solely, or in combination with problematic illicit substance use. In reporting our findings, we have used the terms "heavy drinking" and "substance use" broadly to cover the various ways in which the exposures were defined, although these were not necessarily the terms used by the authors of the studies.

Results

Study characteristics

The 91 studies were conducted in seven countries, with the vast majority (n = 78) carried out in the Nordic region. Studies were published between 1976 and 2019. Nearly two thirds were published since 2010 (n = 60), and, of these, 44 were published since 2015. Approximately 87% of the studies (n = 79) had a sole focus on outcomes of children of heavy drinkers. Spouses/partners were the sole focus of two studies. More than one first-degree relative (i.e., children, siblings, parents) was the focus of seven studies, and unspecified family members were the focus of three studies. In 23 of the 91 studies, familial substance use was the primary explanatory variable under investigation, as opposed to one of several risk factors (Supplemental Table A). Heavy drinking was considered a unique exposure in 49 studies, and the remaining 42 studies combined heavy drinking and illicit drug use into a single exposure category (Supplemental Table B).

Exposure measures

There was considerable heterogeneity in the sources used to assess heavy drinking. The majority of studies, however, used at least one register-based measure. Hospital registers as the sole information source were used by 41 studies. These studies defined a heavy drinker as an individual with a hospital admission for an alcohol-related diagnosis, including, for example, alcohol abuse, alcohol dependence, accidental alcohol poisoning, and/or alcoholic cirrhosis of the liver. Informant reports as the sole information source were used by 13 studies; for example, respondents were asked to report whether a family member was a heavy drinker. The various combinations of information sources are presented in Supplemental Table C.

Outcome measures

The register-based outcomes for family members of heavy drinkers covered a range of areas (Supplemental Table D). Mental health outcomes were the most common, followed by mortality (including suicide) and criminal activity. Studies operationalized mental health outcomes as a diagnosis of a mental disorder recorded in an inpatient or outpatient care register or as a purchase of medication intended for the treatment of mental disorders as recorded in a register of prescription medicines. Mortality was defined based on a recorded death in a cause-of-death register. Criminal activity was operationalized as a conviction recorded in a criminal offenses register. Some studies distinguished between categories of crime, such as violent crimes, and others investigated recidivism.

Employment/financial outcomes, physical health conditions, and out-of-home placements were less common, but still comprised approximately 10% of the studies. Employment/financial outcomes consisted of registrations related to periods of unemployment, receipt of social benefits, and disability pensions recorded in registers of labor market participation and social insurance. Outcomes related to physical health were defined as a hospitalization for an injury or disease, based on the International Classification of Diseases (ICD) diagnosis codes and recorded in a patient register, a registration in a clinical disease register, or by sick leave registrations in a national health insurance register. Other outcomes are summarized and described in Supplemental Tables B and D.

Main findings: Studies with substance use as primary explanatory variable

This section summarizes findings in selected outcome areas of the subgroup of 23 studies in which familial substance use was the primary explanatory variable (Table 1) (results and additional outcomes available in Supplemental Table E).

Mental disorders. Of the five studies that assessed risk of nonspecific mental disorders, four studies found that parental substance use was associated with some measure of increased risk (Jääskeläinen et al., 2016; Martikainen et al., 2018; Raitasalo & Holmila, 2017; Raitasalo et al., 2019); however, in two of these studies, the results were mixed. Jääskeläinen et al. (2016) found that parental substance use increased the odds of adolescent mental disorders, but not mental disorders in mid-childhood. Raitasalo et al. (2019) found that both less severe and severe heavy drinking in mothers increased the risk of mental and behavioral disorders in their children compared with children of non-heavy-drinking mothers; but, for fathers, there was only an increased risk for severe heavy drinking. Findings for specific mental disorders are presented in Table 1 and Supple-

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| Area of harm | Number of studies included (alcohol only/ alcohol + other substances) | Countries | Analysis type (Bivariate Multivariate) | Main findings |
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| Nonspecific psychological illness | 5 (2/3) | Denmark (1) Finland (4) | Multivariate | Four of five studies found some significant association between parental substance use and offspring psychiatric morbidity (Jääskeläinen et al., 2016; Martikainen et al., 2018; Raitasalo & Holmila, 2017; Raitasalo et al., 2019). |
| Mood disorders | 1 (1/0) | Finland | Multivariate | Maternal severe heavy drinking increased children's risk of mood disorders; no significant increased risk for paternal heavy drinking (Raitasalo et al., 2019). |
| Neurotic disorders | 1 (1/0) | Finland | Multivariate | Maternal severe heavy drinking increased children's risk of neurotic, stress-related, and somatoform disorders; no significant increased risk for paternal heavy drinking (Raitasalo et al., 2019). |
| Disorders of psychological development | 2 (2/0) | Finland Sweden | Multivariate | Mixed results, with one study showing no significant increased risk for disorders of psychological development among children of heavy drinkers (Raitasalo et al., 2019) and one showing significant increased risk of autism (Sundquist et al., 2014). |
| Behavioral and emotional disorders | 3 (3/0) | Finland (1) Sweden (2) | Multivariate | All studies showed some increased risk of behavioral and emotional disorders, such as attention deficit/hyperactivity disorder, for children of parents with heavy drinking (Long et al., 2018; Raitasalo et al., 2019; Sundquist et al., 2014). |
| Infant and child mortality | 2 (2/0) | Australia United States | Multivariate | Maternal heavy drinking increased risk for sudden infant death syndrome and other causes of infant mortality (O'Leary et al., 2013) and child death (McCutcheon et al., 2019). |
| Adult and young adult mortality | 4 (4/0) | Denmark (2) Sweden (1) United States (1) | Multivariate | Mixed findings depending on cause of death. |
| Criminality | 6 (6/0) | Denmark (1) Australia (1) Sweden (4) | Multivariate (3) Bivariate (3) | Five studies found significant differences in recorded convictions between children exposed to parental heavy drinking and controls (Christoffersen & Soothill, 2003; Hafekost et al., 2017c; Long et al., 2018; Müitzell, 1994; Rydelius, 1981). |
| Employment | 4 (4/0) | Denmark (1) Sweden (3) | Multivariate (1) Bivariate (3) | Parental heavy drinking associated with increased risk of youth unemployment (Christoffersen & Soothill, 2003). |
| Abuse/neglect | 2 (2/0) | Denmark Australia | Multivariate | Parental heavy drinking associated with increased risk of child being a victim of violence (Christoffersen & Soothill, 2003) and of maltreatment (Hafekost et al., 2017). |
| Placement in residential or foster care | 6 (6/0) | Denmark (1) Australia (1) Finland (1) Sweden (3) | Multivariate (3) Bivariate (3) | Parental heavy drinking associated with increased risk of child's placement in residential or foster care (Christoffersen & Soothill, 2003; Hafekost et al., 2017a; Müitzell, 1994; Müitzell, 1995; Raitasalo et al., 2015; Rydelius, 1981). |
| Education | 3 (3/0) | Sweden (1) Australia (2) | Multivariate | Parental heavy drinking associated with poorer school performance and attendance among offspring (Berg et al., 2016; Hafekost et al., 2017b; Johnson et al., 2017) |
| Disease and injury hospitalizations | 4 (3/1) | Finland (3) Australia (1) | Multivariate | Increased risk of hospital admission among the children of substance-using parents (O'Leary & Slack-Smith, 2013; Raitasalo & Holmila, 2017; Raitasalo et al., 2015; Winqvist et al., 2007) |
| Teenage pregnancy | 1 (1/0) | Denmark | Multivariate | Parental heavy drinking associated with increased risk of teenage motherhood (Christoffersen & Soothill, 2003). |
| Child welfare | 3 (3/0) | Sweden | Bivariate | Significant differences between offspring of heavy drinking parents and controls in terms of registrations for child welfare (Müitzell, 1994, 1995; Rydelius, 1981). |
| Suicide attempts | 1 (1/0) | Denmark | Multivariate | Parental heavy drinking not associated with increased risk of suicide attempts (Christoffersen & Soothill, 2003). |

mental Table E; these results generally show a similar trend to nonspecific mental disorders.

Mortality. Two studies that investigated infant and child mortality found that maternal heavy drinking was associated with an increased risk of offspring death (McCutcheon et al., 2019; O'Leary et al., 2013). Among the four studies that examined young adult or adult mortality, two found a higher risk of death during the follow-up period among family members of heavy drinkers (Christoffersen & Soothill, 2003; Rogers et al., 2016). One study found no significant association between father's alcohol consumption and risk of suicide or other types of violent mortality, and, for total mortality, found mixed results depending on paternal drinking frequency (Landberg et al., 2018).

Of note, Rogers et al. (2016) was the only study among the 23 studies with substance use as the primary explanatory variable that was not restricted to the parent–child relationship. By including various relationships (i.e., a parent, sibling, or other relative), this study assessed different forms of dose-response and showed elevated risk regarding number of heavy drinkers lived with, years lived with the heavy drinker, and relationship to the drinker, with parental heavy drinking exerting a larger influence than the heavy drinking of other relatives (Rogers et al., 2016).

Criminality. Regarding recorded convictions, five of the six studies that investigated criminality found some significant difference between children exposed to parental heavy drinking and those who were not (Christoffersen & Soothill, 2003; Hafekost et al., 2017c; Long et al., 2018; Müitzell, 1994; Rydelius, 1981). One of these studies found significant differences only among male offspring (Rydelius, 1981).

Education. Three studies investigated educational attainment and found poorer outcomes for children of heavy drinkers in terms of school performance or attendance (Berg et al., 2016; Hafekost et al., 2017b; Johnson et al., 2017). However, in one study (Berg et al., 2016), most of the effects were attributed to co-occurring family psychosocial circumstances.

Abuse and/or neglect and placement in residential or foster care. Both studies that looked at abuse/neglect found a significant association, with one showing that parental heavy drinking was associated with an increased risk of a child being a victim of violence (Christoffersen & Soothill, 2003) and the other showing a significantly increased risk of maltreatment (Hafekost et al., 2017a).

Six studies investigated risk of placement in residential or foster care, and all found significant differences between children of heavy drinking parents and controls (Christoffersen & Soothill, 2003; Hafekost et al., 2017a; Müitzell, 1994, 1995; Raitasalo et al., 2015; Rydelius, 1981). In two early studies, however, the difference was only significant among male offspring (Müitzell, 1995; Rydelius, 1981). Raitasalo et al. (2015) investigated risk of heavy drinking and illicit drug use as separate and combined exposures and found the highest risk among children of mothers with combined substance use.

Disease and injury hospitalizations. All four studies of physical illness and injury hospitalizations showed an increased risk among the children of substance-using parents (O'Leary & Slack-Smith, 2013; Raitasalo & Holmila, 2017; Raitasalo et al., 2015; Winqvist et al., 2007). Again, when looking at parental use of different substance categories independently and in combination, Raitasalo et al. (2015) found the highest risk for combined parental alcohol and illicit drug use.

Discussion

This review shows that, overall, register-based research on alcohol-related harms to family members has focused mainly on children of heavy drinkers, with only a small proportion having examined other household relations. Much of this research has drawn upon hospital records to identify heavy drinkers, and most studies have investigated a range of risk factors rather than having heavy drinking as a primary focus.

The fact that nearly all research focused on children as victims of family members' heavy drinking is somewhat surprising, given that prior survey research indicates that having a spouse with an alcohol problem is associated with an increased risk for psychological disorders, mental distress, victimization, and injury (Dawson et al., 2007; Rognmo et al., 2013) and that alcohol is a risk factor for intimate partner violence (Abramsky et al., 2011). On the other hand, this result makes sense in that conducting survey research on children is challenging (Einarsdóttir, 2007), making registerbased research an attractive alternative. Because registerbased studies use existing data and do not require active participation of the research subject, they may be particularly apt for exploring alcohol's harms to children.

Record linkage, in which a register-based measure of exposure is linked with another register-based outcome, was used overwhelmingly by the studies. This means that the alcohol problems of the drinker needed to be sufficiently large to produce, for example, a record of a hospitalization, death, or criminal offense due to an alcohol-related cause. This approach captures mainly the more extreme end of the spectrum of harmful and hazardous alcohol use (Babor et al., 2001; Saha et al., 2006), and thus studies that rely solely on register-based definitions of exposure will capture a fraction of the total cases (Miettunen et al., 2011). Furthermore, alcohol-related disorders are particularly stigmatized conditions (Schomerus et al., 2011) and therefore may be underreported in administrative data, for example, as a cause of death (Cipriani et al., 2001; Rehm et al., 2017).

General population surveys investigating alcohol's harms to children have captured some of the same domains covered by studies included in this review, such as physical health and abuse/neglect. These areas have been probed using survey questions, such as, "In the last 12 months, has one or more of the children who you are responsible for . . . been left in an unsupervised or unsafe situation/been velled at, criticized or otherwise verbally abused/been physically hurt/ witnessed serious violence in the home . . . because of someone's drinking?" (Laslett et al., 2019). In addition to assuming attribution of a causal link between heavy drinking and harm inherent in such survey items, the questions require some level of interpretation of the outcome on the part of the adult respondent. Surveys investigating alcohol's harms to family members also include sensitive questions and therefore may risk underreporting by participants (Tourangeau & Yan, 2007). On the other hand, register-based studies have addressed these domains by targeting highly specific and precisely defined harms. For instance, hospitalizations because of injuries, illness, or psychiatric disorder diagnoses are recorded in healthcare registers (Raitasalo & Holmila, 2017), and the association with heavy drinking is made by linking registers.

The findings from the current review are generally consistent with previous reviews of largely non-register-based studies, which demonstrate increased psychosocial problems among children exposed to parental substance use (Harter, 2000; Kuppens et al., 2020; Rossow et al., 2016). However, the present focus on register-based studies offers a unique contribution. As demonstrated in this review, register-based studies can inform on specific harms, such as precise diagnostic categories in the areas of physical and mental health (O'Leary & Slack-Smith, 2013; Raitasalo et al., 2015, 2019). The large sample sizes in most register-based studies also ensure adequate power to detect a hypothesized effect, which may be lacking when using other study designs (Harter, 2000).

The use of registers allows for tracking children from birth through adolescence and beyond. Studies included in previous reviews tended to focus on the adolescent period, or, when young children were included, they had a narrow emphasis on externalizing and internalizing problems (Kuppens et al., 2020; Rossow et al., 2016). In contrast, studies included in the current review cover a range of physical and mental health outcomes also among very young children (e.g., O'Leary & Slack-Smith, 2013; Raitasalo & Holmila, 2017). The use of register data also allows for testing theorybased hypotheses regarding the contribution of biological factors, for example, by looking at effects of timing of alcohol use disorder diagnoses in relation to pregnancy, or by separating socialization from genetic mechanisms by examining "lived with" versus "not lived with" immediate family members (Hafekost et al. 2017b; Long et al., 2018; O'Leary et al., 2013; Raitasalo & Holmila, 2017).

Although the causal pathways connecting alcohol and adverse outcomes for family members will likely include both genetic and environmental mechanisms, the relative strengths of influence of such mechanisms may differ depending on the outcome. Therefore, using register data to separate the effects of living with heavy drinkers from those of being genetically related to them represents an important contribution (Kendler et al., 2015b; Khemiri et al., 2020).

Limitations

To provide an overview of existing register-based research, this scoping review has covered a heterogeneous group of studies with varying population sizes, follow-up periods, definitions of exposures and outcomes, and covariates. However, this heterogeneity limited us to using a vote-counting procedure, which is not ideal for summarizing findings across studies (Higgins et al., 2019). Furthermore, as this review aimed to cast a wide net to identify all register-based studies of alcohol's harms to family members, studies were included that did not distinguish between heavy drinking and illicit drug use.

Other than a recent meta-analysis of longitudinal studies investigating the association between parental substance use and various domains of child well-being (Kuppens et al., 2020), we are unaware of a substantial body of research comparing effects of alcohol and drug use on family members. Differences in the legal status of the substances could have an influence on the harms to family members; for instance, Kuppens et al. (2020) found a stronger association for illicit drug use compared with heavy drinking. Thus, there could be some concern about our ability to draw conclusions about heavy drinking as a unique exposure. However, 87% of the studies for which specific findings were presented included heavy drinking as a single exposure. Moreover, heavy drinking was an independent study exposure in 14 of the 16 areas of harm described in Table 1.

Since our search strategy prioritized household family members, some studies investigating harms to extended family members may have been missed. Such studies could have permitted a dose-response analysis—an examination of whether there is a gradation of the effect, such that family members more immediately connected to the drinker experience a greater degree of harm (Rogers et al., 2016).

Conclusions and future research

Survey- and register-based methodologies can be seen as complementary. Whereas surveys can cover less severe, less tangible, and perhaps shorter term outcomes, register-based methods address more serious, persistent, and rare outcomes. Consideration of findings from these diverse methodologies represents an opportunity for a triangulation of data, wherein multiple data sources are used to verify and complement findings or point to inconsistencies in existing research.

This review demonstrates that a large body of registerbased research has been produced on the topic of alcohol's harms to children of parents with the most severe alcohol problems. Findings demonstrate increased risk in areas such as hospitalizations for illness and injuries (Raitasalo et al., 2015), mental health diagnoses (Long et al., 2018; Raitasalo et al., 2019; Sundquist et al., 2014), convictions (Christoffersen & Soothill, 2003; Hafekost et al., 2017c; Long et al., 2018), and poor school performance and attendance (Berg et al., 2016; Hafekost et al., 2017b; Johnson et al., 2017).

Future research could assess the impact of alcohol use on household relations other than children of heavy drinkers. Whereas it may be burdensome to assess the experiences of both drinkers and family members using survey methods, population registers allow for the linking of parents, children, partners, and siblings, providing relatively easy access to existing data on relatives. In this way, researchers may explore the extent to which alcohol's harms to others has permeated family life.

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Contents lists available at ScienceDirect

Drug and Alcohol Dependence





Hazardous drinking and violence-related hospitalizations in the Danish general population: A historical cohort study



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ARTICLE INFO

Keywords: Alcohol Cohort Hospitalization Registries Victimization Violence

ABSTRACT

Background: It is well documented by case-control and case-crossover studies that hazardous drinking and the risk of experiencing violence-related injuries are related. The present study investigated this relationship in a cohort of general population survey respondents in Denmark using subsequent hospital admissions for violence. *Methods:* The cohort consisted of participants in the 2011 Danish national survey on alcohol and drugs (N = 5126). Survey responses were used to identify those with hazardous alcohol use. Register data on the cohort's hospital admissions for violence from 2010 through 2018 served as the outcome. The relationship between respondents' hazardous drinking and counts of subsequent hospital admissions was investigated using a Poisson regression model.

Results: After controlling for confounding, respondents with hazardous consumption (Alcohol Use Disorders Identification Test Consumption [AUDIT-C] cut off: 5 points) had an increased rate of hospital admissions for violence, with an incidence rate ratio (IRR) of 2.28 (95% CI: 1.16–4.50) compared to respondents without hazardous alcohol use. Each additional AUDIT-C point was associated with a 20% increase in the incidence rate for violence-related admission (IRR=1.20, 95% CI: 1.06–1.37). Furthermore, interaction analyses showed a significant interaction between gender and AUDIT-C score on hospital admissions for violence (IRR=0.69, 95% CI: 0.53–0.90).

Conclusions: Results provide evidence that hazardous alcohol use is associated with subsequent hospital admissions for violence in the Danish general population and that gender moderates this relationship.

1. Introduction

Intentional injuries, which consist of injuries sustained from nonaccidental causes, including self-inflicted injuries and violence (Murray et al., 2001), are a leading cause of death and disability among young people (GBD, 2019 Diseases and Injuries Collaborators, 2020). The relationship between alcohol consumption and risk of intentional injuries for the drinker has been well documented by case-control and case-crossover studies (Cherpitel, 2007; Devries et al., 2014; Taylor et al., 2010; Vinson et al., 2003) as well as some longitudinal studies (e. g., Thompson et al., 2008). The role of both acute and chronic alcohol use in fatal violence-related injuries has also been a focus of prior research. Alcohol intoxication is common among homicide victims (Kuhns et al., 2011; Naimi et al., 2016), and population-based studies from the Nordic countries have shown that having an alcohol or a substance use disorder diagnosis is associated with an increased risk of homicide victimization (Crump et al., 2013; Hiroeh et al., 2001).

Previous studies of alcohol and violence have drawn study samples from emergency departments (Cherpitel, 2007; Zerhouni et al., 2013) and from hospital registers (Murphy et al., 2019). The current study builds on the existing body of research by using a methodology which links general population survey data on drinking with longitudinal

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https://doi.org/10.1016/j.drugalcdep.2022.109338

Received 14 October 2021; Received in revised form 4 January 2022; Accepted 23 January 2022 Available online 29 January 2022

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hospital records on violence. In contrast to administrative data, general population survey data are likely to identify individuals with lower rates of consumption and alcohol-related problems, while at the same time providing a detailed view of drinking behaviors across different levels and patterns of drinking. On the other hand, hospital registers offer some advantages in capturing instances of victimization, as they allow for the measurement of violence-related injuries over time and are less susceptible to nonresponse biases that may affect victimization surveys (Kruse et al., 2010; McNutt and Lee, 2000).

Sociodemographic variables, such as gender, age and socioeconomic status (SES) have been shown to modify the effect of alcohol consumption on a broad range of outcomes (Grittner et al., 2012; Katikireddi et al., 2017; Knott et al., 2015; Stockwell et al., 2002). These factors also have a direct effect on violent victimization, with a higher risk of victimization among men, young adults and people of lower SES (Bellis et al., 2008, 2011).

In terms of the relationship between alcohol consumption and violence victimization, there is some prior work investigating differential effects of alcohol consumption by sociodemographic variables, particularly gender, with studies showing that among respondents who had been physically assaulted, men were more likely to have been drinking during the incident than women (Scott et al., 1999) and that drinking plays a stronger role in the risk of experiencing victimization among men compared to women (Ellonen and Aaltonen, 2012; Felson and Burchfield, 2004). However, some studies that have included interaction analyses have not found the difference in effect sizes between men and women to be significant (Korcha et al., 2014). Variation across other sociodemographic factors in the relationship between alcohol measures and victimization has been less frequently explored, although some previous research has shown that drinking has a greater effect on the risk of experiencing violence victimization among young adults compared to older adults (Felson and Burchfield, 2004).

In Denmark, like in other Western countries, men tend to drink more than women (Grittner et al., 2020). Recent Danish national survey results show the proportion exceeding the high-risk drinking thresholds defined by the Danish Health Authority (> 14 drinks per week for women; > 21 drinks per week for men) (Danish Health Authority, 2019) is highest among those ages 16–24, but also elevated among those ages 55–74 (Jensen et al., 2018).

Findings regarding the relationship between SES and alcohol consumption in Denmark have varied. Some studies have found no evidence that drinking patterns differ substantially by SES (Bloomfield et al., 2008; Seid et al., 2018), while others have shown people of higher SES were more likely to drink heavily (Hansen et al., 2011). As regards the effect of SES on alcohol-related harm, a recent study of alcohol-related liver disease found strong evidence of a socio-economic gradient in Denmark (Askgaard et al., 2021). However, studies of alcohol's harms to others have been mixed, with one study finding level of education modified the relationship between one's own alcohol consumption and experience of harassment by someone who has been drinking (Beckhoff et al., 2020), while another did not find evidence that SES affected the relationship between parental alcohol problems and young people's emotional problems and depression (Pisinger and Tolstrup, 2021). In summary, the link between alcohol consumption and harm may differ between sociodemographic population subgroups, depending on the outcomes considered and the overall drinking pattern in a given group.

The aim of the current study was to examine whether hazardous drinking as measured in a general population survey sample is associated with a subsequent increased rate of hospitalization for violence. A further focus was to investigate whether the relationship between hazardous drinking and later hospital admission for violence is modified by sociodemographic factors.

2. Material and methods

2.1. Study design and population

This is a historical cohort study in which the cohort consists of respondents to the cross-sectional 2011 Danish National Alcohol and Drug Survey (Bloomfield et al., 2013). The survey was completed via a telephone or Web questionnaire and conducted by Statistics Denmark on behalf of the Centre for Alcohol and Drug Research, Aarhus University. From the initial sample of 8004 residents (ages 15–79) randomly selected from the Danish civil registration system who received a mailed invitation, 5133 (64%) participated in the survey, and 5126 provided sufficient information to calculate Alcohol Use Disorders Identification Test Consumption (AUDIT-C) scores (Bush et al., 1998). The cohort was followed from September 2010 until the end of 2018.

Oral or written informed consent was given by the respondents before participation in the survey. Ethical approval of the survey study was provided by the Danish Data Protection Agency. Since the register data used for this study were collected and stored for monitoring and quality assurance in Denmark, no ethics evaluation for use of register data was needed under Danish law. All data were kept on secure servers at Statistics Denmark.

Each individual officially residing in Denmark is assigned a unique personal identification number, which allows for linkages between different registers (Pedersen et al., 2006) and, in the present study, also between survey data and register data. For censoring purposes, mortality data on the cohort were extracted from the causes-of-death register, and emigration status was determined based on presence in the population register with the date of emigration out of Denmark assigned as December 31st of the subsequent year the individual was last recorded in the population register (Helweg-Larsen, 2011; Statistics Denmark, 2021).

2.2. Measures/variables

2.2.1. Alcohol-related exposure

Hazardous alcohol consumption was measured by the AUDIT-C questionnaire (Bush et al., 1998), which was included in the 2011 survey. The AUDIT-C is a subset of the AUDIT (Babor et al., 2001), which comprises three questions on frequency of drinking, amount of alcohol consumed, and frequency of heavy episodic drinking during the past 12 months, scored on a scale of 0–12 points. It is a validated screening tool for detecting heavy/risk drinking and alcohol abuse or dependence (Bush et al., 1998; Campbell and Maisto, 2018; Dawson et al., 2005). In the present study, the AUDIT-C was selected over the full AUDIT in order to avoid confounding exposure and outcome. Additional questions in the full AUDIT measure consequences and dependence on alcohol (including health and social problems caused by drinking) and thus could potentially overlap with the outcome in this study. Therefore, by using the AUDIT-C, we use an established indicator of hazardous drinking that keeps the exposure and outcome variables distinct.

Using a recommended cut-off for general population samples (Rumpf et al., 2002), participants were divided into two groups: AUDIT-C score of 0–4 and AUDIT-C score of 5 or higher. In order to assess a dose-response relationship, we also conducted analyses with AUDIT-C score and scores for each of the three AUDIT-C items separately as continuous variables.

2.2.2. Outcome

The outcome was the number of hospital admissions for violence. These data were identified through data linkage with the Danish National Patient Registry (NPR) (Schmidt et al., 2015). The NPR contains information on patient contacts with hospital departments in Denmark since 1977; since 1995, the NPR also includes information from emergency departments, psychiatric departments, and outpatient clinics (Lynge et al., 2011). The NPR includes an International Classification of Diseases (ICD-10) code specifying the primary diagnosis in relation to the hospital contact, and, in relevant cases, additional diagnoses. The register also includes a variable specifying the reason for the emergency department contact (Schmidt et al., 2015). In the NPR, these reasons are used in lieu of an ICD code specifying the external cause of morbidity (Kruse et al., 2010). The reason-for-contact codes are assigned at admission by emergency department staff and include the following: Illness without direct relation to external lesion; Accident; Act of violence; Suicide, suicide attempt, or self-inflicted harm; Sequelae. For admissions with an external cause of injury, the Nordic Medico-Statistical Committee (NOMESCO) Classification of External Causes of Injuries (NCECI) is used (Laursen and Møller, 2011). According to NCECI, violence is defined as "assault by other person resulting in injury", including assault, brawl, maltreatment and sexual assault (Nordic Medico-Statistical Committee, 2007). In this study, the outcome was any hospital admission with a reason for contact specified as violence during the eight-year follow-up period. For each individual, all admissions that included violence as a reason for contact during the follow-up period were included. However, as each admission should reflect a distinct episode of violence victimization, any admissions that occurred on the same day were collapsed into a single episode.

2.2.3. Covariates

Covariates included gender, ethnicity, highest level of education, age, prior psychiatric disorders, past-year illicit drug use, respondent's cohabitation status, and presence of minor children in the home. Gender was recorded as male or female based on the participant's response in the survey. Ethnicity was drawn from the population register and was defined based on the standard definitions used by Statistics Denmark: individuals who were of Danish origin, and individuals who were immigrants or who had two non-Danish-citizen parents. Highest level of education was drawn from the Highest Completed Education register (Jensen and Rasmussen, 2011), and it was categorized into low (compulsory education), medium (vocational or upper secondary education) and high (higher education). For the interaction analysis, level of education was dichotomized (low and medium versus high). Age was reported by the respondent at the time of the survey and was included as a continuous variable in the regression analysis and a four-category variable in the descriptive analysis.

A respondent was considered to have a prior psychiatric disorder if they received any of the following ICD-10 diagnoses in the NPR prior to 1 September 2010: F2 (schizophrenia, schizotypal and delusional disorders), F3 (mood disorders), F4 (neurotic, stress-related and somatoform disorders), or F6 (disorders of adult personality and behavior). Illicit drug use was identified based on responses to the 2011 survey. A respondent who reported that they had used cannabis resin, cocaine, amphetamines, ecstasy, solvents, hallucinogens, heroin, or other opiates (methadone, opium, or morphine) in the past 12 months was considered to have used illicit drugs.

A respondent's cohabitation status was categorized as either single or living with a partner. Respondents were considered to be living with a partner if they either indicated they were married/living with partner in the 2011 survey or if they were registered as part of a couple in the population register in 2011. Presence of children (under 18 years) in the household was determined based on responses to the 2011 survey.

2.3. Statistical methods

Using register data, respondents from the 2011 survey were followed starting from 1 September 2010. This date was chosen as it begins the approximate reference period covered by the survey (i.e., respondents were queried about the 12 months prior to survey administration). At the time the study was carried out, register data were available through 2018. Thus, follow-up continued until the end of the study on 31 December 2018, emigration, or death, whichever came first.

Cross-tabulations with corrected, weighted χ^2 tests were used to

Table 1

Study population characteristics by AUDIT-C status.

| | Overall, n | AUDIT-C < 5, weighted % | AUDIT-C \geq 5, weighted % | Design-based F statistic ^a |
|---|---------------|-------------------------------|------------------------------|--|
| Total | 5126 | 55.69 | 44.31 | |
| Gender | 0120 | 00103 | 11101 | |
| Male | 2420 | 43.45 | 56.55 | $F(1, 5125) = 281.20^{b}$ |
| Female Ethnicity | 2706 | 67.87 | 32.13 | |
| Danish origin | 4780 | 53.49 | 46.51 | $F(1, 5125) = 54.46^{b}$ |
| Immigrant/ descendent ^c | 346 | 74.45 | 25.55 | |
| Age group | | | | |
| 15-29 | 1136 | 35.53 | 64.47 | F(2.99, |
| 30-45 | 1308 | 62.75 | 37.25 | 15,318.67)= |
| 46-64 | 1820 | 58.52 | 41.48 | 83.78 ^b |
| 65+ | 862 | 67.37 | 32.63 | |
| Highest level of education ^{d,e} | | | | |
| Low | 951 | 64.72 | 35.28 | F(1.98, 10,086.04)= 23.21 ^b |
| Medium | 2123 | 53.25 | 46.75 | |
| High | 2011 | 52.18 | 47.82 | |
| Past-year illicit drug use ^f | | | | |
| No | 4820 | 58.04 | 41.96 | $F(1, 5113) = 123.38^{b}$ |
| Yes Prior psychiatric disorder diagnosis | 294 | 22.29 | 77.71 | |
| No | 4888 | 55.56 | 44.44 | F(1, 5125) = 0.48 |
| Yes Cohabitation status | 238 | 57.95 | 42.05 | |
| Living with partner | 3647 | 58.68 | 41.32 | $F(1, 5125) = 32.00^{b}$ |
| Single Children <18 in | 1479 | 49.62 | 50.38 | |
| No | 3478 | 51.75 | 48.25 | $F(1, 5062) = 71.71^{b}$ |
| Vec | 1585 | 65.13 | 34 87 | |

Notes: AUDIT-C=Alcohol Use Disorders Identification Test-Consumption.

^a Corrected, weighted.

^b p-value < 0.001.

^c Individuals who were immigrants or who had two non-Danish-citizen parents.

^d Missing data for 41 respondents.

^e Low=compulsory education, Medium=Upper secondary education or vocational training, High=higher education.

^f Missing data for 12 respondents.

^g Missing data for 63 respondents.

examine bivariate associations between AUDIT-C scores and the covariates. Based on the Bayesian information criterion (BIC) and the Akaike information criterion (AIC), Poisson regression was chosen for multivariate modeling. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were calculated using follow-up time as an exposure variable in the regression model. AUDIT-C was first included as a dichotomous indicator of heavy drinking. Then, to test for a doseresponse relationship, the continuous AUDIT-C total score was used. Additional analyses used each of the individual AUDIT-C items separately. After the main effects were assessed, interactions of hazardous drinking with age, gender, and SES were included separately in multivariate regressions. In cases of significant interaction effects, the predictive margins for the moderating variable were graphed to illustrate the relationship between hazardous drinking and hospital admissions

Table 2

Adjusted incidence rate ratios (95% CIs) for Poisson regression predicting hospital admissions for violence using AUDIT-C cutoff (<5 vs. 5 + points) (weighted; unweighted N = 5126).

| | Main effects model | | Interaction model 1 | | Interaction model 2 | | Interaction model 3 | |
|-----------------------------------|---------------------------|-------|---------------------------|-------|---------------------------|-------|---------------------------|-------|
| Variable | IRR ^a (95% CI) | Р | IRR ^b (95% CI) | Р | IRR ^c (95% CI) | Р | IRR ^d (95% CI) | Р |
| MAIN EFFECTS | | | | | | | | |
| Hazardous drinking status | | | | | | | | |
| AUDIT-C< 5 | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| AUDIT-C \geq 5 | 2.28 (1.16-4.50) | 0.017 | 3.95 (1.23-12.71) | 0.021 | 3.52 (1.01-12.27) | 0.048 | 1.82 (0.51-6.48) | 0.353 |
| Gender | | | | | | | | |
| Men | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Women | 0.61 (0.33-1.11) | 0.107 | 1.44 (0.41-5.06) | 0.566 | 0.60 (0.33-1.08) | 0.089 | 0.62 (0.34-1.13) | 0.118 |
| Ethnicity | | | | | | | | |
| Danish origin | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Immigrant/descendent ^e | 1.21 (0.46-3.18) | 0.704 | 1.21 (0.46-3.21) | 0.704 | 1.23 (0.47-3.23) | 0.674 | 1.23 (0.47-3.21) | 0.671 |
| Age (years) | 0.94 (0.92-0.96) | < | 0.94 (0.92–0.96) | < | 0.95 (0.93-0.97) | < | 0.94 (0.93–0.96) | < |
| | | 0.001 | | 0.001 | | 0.001 | | 0.001 |
| Level of education ^f | | | | | | | | |
| High | 1 (ref) | | 1 (ref) | | 1 (ref) | | | |
| Medium | 1.88 (0.91-3.86) | 0.086 | 1.86 (0.90-3.82) | 0.092 | 1.87 (0.91-3.85) | 0.088 | | |
| Low | 3.68 (1.56-8.67) | 0.003 | 3.72 (1.59-8.72) | 0.002 | 3.67 (1.56-8.63) | 0.003 | | |
| Cohabitation status | | | | | | | | |
| Living with partner | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Single | 0.93 (0.42-2.07) | 0.863 | 0.94 (0.42-2.07) | 0.869 | 0.93 (0.42-2.06) | 0.858 | 0.95 (0.43-2.11) | 0.906 |
| Children < 18 in home | | | | | | | | |
| No | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Yes | 0.71 (0.30-1.67) | 0.431 | 0.69 (0.30-1.62) | 0.397 | 0.72 (0.30-1.71) | 0.455 | 0.70 (0.30-1.67) | 0.425 |
| Past-year illicit drug use | | | | | | | | |
| No | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Yes | 1.83 (0.93–3.59) | 0.079 | 1.76 (0.89–3.47) | 0.106 | 1.80 (0.92-3.53) | 0.087 | 1.93 (0.99–3.77) | 0.054 |
| Prior psychiatric disorder | | | | | | | | |
| diagnosis | | | | | | | | |
| No | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Yes | 1.07 (0.33-3.46) | 0.912 | 1.06 (0.33-3.44) | 0.918 | 1.08 (0.33-3.53) | 0.893 | 1.19 (0.38–3.77) | 0.768 |
| Any higher education | | | | | | | | |
| Yes | | | | | | | 1 (ref) | |
| No | | | | | | | 1.95 (0.51–7.53) | 0.332 |
| INTERACTIONS | | | | | | | | |
| AUDIT-C*Gender | | | 0.28 (0.06-1.27) | 0.099 | | | | |
| AUDIT-C*Age | | | | | 0.99 (0.96-1.02) | 0.404 | | |
| AUDIT-C*Any higher education | | | | | | | 1.28 (0.28-5.91) | 0.755 |

Notes: AUDIT-C=Alcohol Use Disorders Identification Test-Consumption; IRR = incidence rate ratio; CI = confidence interval

^a Model includes hazardous drinking status, gender, ethnicity, age, highest level of education, cohabitation status, children < 18 living in the home, past-year illicit drug use, and prior psychiatric diagnosis.

^b Model includes hazardous drinking status, gender, ethnicity, age, highest level of education, cohabitation status, children < 18 living in the home, past-year illicit drug use, prior psychiatric diagnosis, and AUDIT-C*gender interaction.

^c Model includes hazardous drinking status, gender, ethnicity, age, highest level of education, cohabitation status, children < 18 living in the home, past-year illicit drug use, prior psychiatric diagnosis and AUDIT-C*age interaction.

^d Model includes hazardous drinking status, gender, ethnicity, age, any higher education, cohabitation status, children < 18 living in the home, past-year illicit drug use, prior psychiatric diagnosis and AUDIT-C*any higher education interaction.

^e Individuals who were immigrants or who had two non-Danish-citizen parents.

^f High=higher education, Medium=Upper secondary education or vocational training, Low=compulsory education.

for violence across levels of the moderator. All regression analyses applied weights created by Statistics Denmark to reflect the age, gender, family structure, education, income, and country of origin of the national population. Analyses were carried out using STATA v.16 (Stata-Corp, 2019).

3. Results

3.1. Description of participants and outcomes

Table 1 shows 44.31% of respondents had an AUDIT-C score indicating hazardous drinking (AUDIT-C \geq 5). Hazardous drinking was more common among men (56.55%) compared to women (32.13%) and among participants of Danish origin (46.51%) compared to immigrants/ descendants (25.55%). A larger proportion of the youngest age group drank hazardously compared to the other age groups. The proportion of participants with hazardous drinking also was higher among those with a higher level of education, as well as among those who were single, those with past-year illicit drug use, and those without children at home.

The population was followed for an average of 8.14 years. A total of 51 participants (1.15%) had at least one admission due to violence during the follow-up period. Of these, 40 participants reported hazardous drinking on the survey (1.98% of those with AUDIT \geq 5) and 11 reported no hazardous drinking (0.49% of those with AUDIT<5). Fewer than five participants experienced two admissions, and none experienced more than two admissions.

3.2. Multivariate analyses of hospital admissions

In the main effects multivariate model, the rate of hospitalizations for violence was 2.28 times higher [95% CI: 1.16–4.50] for hazardous drinkers than for respondents without hazardous alcohol use (Table 2). Rates of hospitalizations for violence were significantly lower among older respondents compared to younger respondents [IRR 0.94, 95% CI: 0.92–0.96] and significantly higher among those with a low level of education compared to those with higher education [IRR 3.68, 95% CI:

Table 3

Adjusted incidence rate ratios (95% CIs) for Poisson regression predicting hospital admissions for violence using AUDIT-C as a continuous variable (0–12 points) (weighted; unweighted N = 5126).

| | Main effects model | | Interaction model 1 | | Interaction model 2 | | Interaction model 3 | |
|---|---------------------------|---------|---------------------------|---------|---------------------------|-------|---------------------------|---------|
| Variable | IRR ^a (95% CI) | Р | IRR ^b (95% CI) | Р | IRR ^c (95% CI) | Р | IRR ^d (95% CI) | Р |
| MAIN EFFECTS | . , | | . , | | . , | | . , | |
| Hazardous drinking status | | | | | | | | |
| AUDIT-C score | 1.20 (1.06-1.37) | 0.005 | 1.37 (1.18–1.60) | < 0.001 | 1.30 (1.07-1.59) | 0.009 | 1.10 (0.87–1.39) | 0.420 |
| Gender | | | | | | | | |
| Men | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Women | 0.66 (0.37-1.17) | 0.153 | 5.23 (1.19-23.09) | 0.029 | 0.65 (0.37-1.12) | 0.122 | 0.66 (0.37-1.18) | 0.163 |
| Ethnicity | | | | | | | | |
| Danish origin | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Immigrant/descendent ^e | 1.37 (0.53–3.57) | 0.519 | 1.29 (0.50-3.33) | 0.594 | 1.39 (0.53–3.62) | 0.498 | 1.38 (0.53–3.57) | 0.505 |
| Age (years) | 0.94 (0.92–0.96) | < 0.001 | 0.94 (0.92–0.96) | < 0.001 | 0.96 (0.92-1.00) | 0.031 | 0.95 (0.93–0.96) | < 0.001 |
| Level of education ^f | | | | | | | | |
| High | 1 (ref) | | 1 (ref) | | 1 (ref) | | | |
| Medium | 1.90 (0.93-3.90) | 0.079 | 1.89 (0.92–3.87) | 0.084 | 1.90 (0.93–3.89) | 0.080 | | |
| Low | 3.69 (1.58-8.61) | 0.002 | 3.63 (1.55-8.48) | 0.003 | 3.65 (1.55-8.58) | 0.003 | | |
| Cohabitation status | | | | | | | | |
| Living with partner | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Single | 0.90 (0.41-1.99) | 0.800 | 0.87 (0.40-1.89) | 0.732 | 0.90 (0.41-1.97) | 0.784 | 0.93 (0.43-2.04) | 0.862 |
| Children < 18 in home | | | | | | | | |
| No | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Yes | 0.76 (0.33–1.76) | 0.526 | 0.74 (0.32-1.70) | 0.477 | 0.77 (0.33-1.78) | 0.537 | 0.76 (0.33–1.74) | 0.510 |
| Past-year illicit drug use | | | | | | | | |
| No | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Yes | 1.60 (0.79-3.26) | 0.191 | 1.49 (0.72-3.05) | 0.281 | 1.58 (0.79-3.19) | 0.198 | 1.69 (0.83-3.42) | 0.145 |
| Prior psychiatric disorder diagnosis | | | | | | | | |
| No | 1 (ref) | | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Yes | 1.11 (0.35-3.53) | 0.864 | 1.12 (0.36-3.53) | 0.842 | 1.14 (0.35-3.67) | 0.831 | 1.21 (0.39-3.78) | 0.744 |
| Any higher education | | | | | | | | |
| Yes | | | | | | | 1 (ref) | |
| No | | | | | | | 1.17 (0.17-8.19) | 0.878 |
| INTERACTIONS | | | | | | | | |
| AUDIT-C*Gender | | | 0.69 (0.53-0.90) | 0.006 | | | | |
| AUDIT-C*Age | | | | | 1.00 (0.99–1.00) | 0.455 | | |
| AUDIT-C*Any higher education | | | | | | | 1.12 (0.84–1.49) | 0.445 |

Notes: AUDIT-C=Alcohol Use Disorders Identification Test-Consumption; IRR = incidence rate ratio; CI = confidence interval

^a Model includes hazardous drinking status, gender, ethnicity, age, highest level of education, cohabitation status, children < 18 living in the home, past-year illicit drug use, and prior psychiatric diagnosis.

^b Model includes hazardous drinking status, gender, ethnicity, age, highest level of education, cohabitation status, children < 18 living in the home, past-year illicit drug use, prior psychiatric diagnosis, and AUDIT-C*gender interaction.

^c Model includes hazardous drinking status, gender, ethnicity, age, highest level of education, cohabitation status, children < 18 living in the home, past-year illicit drug use, prior psychiatric diagnosis, and AUDIT-C*age interaction.

^d Model includes hazardous drinking status, gender, ethnicity, age, any higher education, cohabitation status, children < 18 living in the home, past-year illicit drug use, prior psychiatric diagnosis, and AUDIT-C*any higher education interaction.

^e Individuals who were immigrants or who had two non-Danish-citizen parents.

^f High=higher education, Medium=Upper secondary education or vocational training, Low=compulsory education.

1.56-8.67].

As shown in Table 3, when used as a continuous variable, there was an increased rate of hospitalizations for violence with increasing AUDIT-C scores (IRR=1.20, 95% CI: 1.06–1.37). There were similar effects of age and education as were observed when AUDIT-C was examined as a cut-off score.

3.3. Interaction analyses

There was a statistically significant interaction between gender and the continuous AUDIT-C score on hospital admissions for violence (IRR=0.69, 95% CI: 0.53–0.90) (Table 3) but not when the dichotomous indicator was used (Table 2). There were no significant interaction effects for level of education or age with AUDIT-C score (Tables 2 and 3).

The interaction of gender and AUDIT-C score is depicted in Fig. 1, which shows the predictive margins by gender. There is a clear doseresponse relationship for men, with each additional AUDIT-C point at the higher end of the spectrum. Analyses of individual AUDIT-C items revealed a similar pattern (Fig. 2). Specifically, for men, increasing AUDIT-C scores, in terms of frequency of drinking, quantity of alcohol consumed, and frequency of heavy drinking, are each associated with a greater number of predicted hospital admissions for violence. For women, the effect of the AUDIT-C score is less clear, with non-drinkers and non-risky drinkers, but also those with more drinks per drinking day, having the highest number of predicted hospitalizations.

4. Discussion

The aim of this study was to assess the relationship between hazardous drinking in the general population and risk of hospital admissions for violence. As predicted, hazardous drinking was indeed associated with increased rate of hospital admissions for violencerelated causes. This finding, which is based on a general population sample, is in line with previous studies of emergency department samples in other countries showing an increased risk of intentional injuries among intoxicated patients (Borges et al., 2008; Macdonald et al., 2006).

Our analysis utilizing survey data for the exposure measurement and register data on hospital admissions due to violence as the outcome measurement offers a unique contribution to the evidence of the alcohol and violence association. Usually, alcohol use surveys contain both the



Fig. 1. Predictive margins by gender (95% CIs) for the interaction between gender and AUDIT-C total score (0–12 points). Fig. 1 shows the predictive margins by gender and AUDIT-C score with 95% CIs. The predicted number of hospital admissions for violence at each combination of gender and AUDIT-C score are plotted. Notes: AUDIT-C=Alcohol Use Disorders Identification Test-Consumption; CI = confidence interval.

measures of alcohol use and questions on predefined alcohol-related consequences (Gmel et al., 2010, 2000). That is, survey respondents are most often presented with questions about the experience of violence as alcohol-related. However, in the present study, the measurement of the outcome variable was independent of the measurement of alcohol use. Thus, our analysis has been able to establish a statistically significant non-biased link that contributes more evidence to this association.

It should also be noted that we found independently significant effects for age and educational attainment. These findings support previous Danish register-based studies showing that younger people (Seid et al., 2021) and those with lower SES (Kruse et al., 2010; Murphy et al., 2019; Seid et al., 2021) experience greater risk of violence victimization.

Gender moderated the effect of AUDIT-C score on violence hospitalization. Predictive margins showed a dose-response of total AUDIT-C score for men but not for women. Other studies have found that compared to men, women are more likely to have been victimized in the home and by partners rather than by strangers (Hofner et al., 2005; Tingne et al., 2014; Wright and Kariya, 1997). Thus, the finding from our study may be explained by considering gender differences in terms of the likely perpetrator and settings of incidents of violence that may result in hospital contact. One possible interpretation is that the type of alcohol-related violent victimization that might best be captured by hospital registers comprises incidents occurring in public and outside of an intimate relationship, such as episodes taking place in drinking establishments, like bars and pubs – locations which have previously been tied to an increased risk for violence (Graham and Homel, 2008). Incidents that occur in such public settings are more likely to be witnessed, perhaps by police or bystanders, and thus the victims may be more likely to be seen in an acute hospital setting.

Gender differences were particularly evident for AUDIT-C scores at the high end of the spectrum, which could explain why the interaction effect was not observed when the dichotomous indicator was used. Analysis of the individual AUDIT-C items gives further insight into the observed gender differences. Women who reported no drinking in the last year had the highest predicted number of events. As drinking is largely a social activity in Denmark (Grønkjær et al., 2010), perhaps this finding reflects that women who abstain do so because they are socially isolated, and thus they may be at greater risk for experiencing violence, possibly by their partner (Mojahed et al., 2021).

We did not find support for an interaction between hazardous drinking and SES in this study, although both variables had significant main effects on hospitalizations for violence. This was an unexpected finding, since the evidence of an interaction between drinking and SES for other health outcomes is otherwise quite robust (Katikireddi et al., 2017; Mäkelä and Paljärvi, 2008; Probst et al., 2014). In all likelihood, we were unable to include some of the most vulnerable people, such as homeless people and those with the most serious alcohol problems, who ostensibly would be at high risk of violent victimization. However, even given this reservation, it appears that at the general population level, the link between hazardous drinking and violent victimization is not specifically limited to those with low SES in Denmark.



Fig. 2. Predictive margins by gender (95% CIs) for the interaction between gender and AUDIT-C individual item scores. Fig. 2 shows the predictive margins with 95% CIs for the interactions of gender and the individual AUDIT-C item scores. The predicted number of hospital admissions for violence at each combination of gender and the scores for each AUDIT-C item are plotted. Item 1 (left) measures frequency (i. e., how often the respondent had a drink containing alcohol); item 2 (in middle) measures quantity (i.e., how many drinks the respondent had on a typical day when they were drinking); and item 3 (right) measures frequency of heavy episodic drinking (i.e., how often the respondent had five or more drinks [one drink=12 g pure alcohol] on one occasion). Notes: AUDIT-C=Alcohol Use Disorders Identification Test-Consumption; CI = confidence interval. For item 1, 0: never; 1: \leq monthly; 2: 2–4 times per month; 3: 2–3 times per week; 4: \geq 4 times per week. For item 2, 0: 1-2; 1: 3-4; 2: 5-6; 3: 7-9 or 4: \geq 10. For item 3, 0: never; 1: < monthly; 2: monthly; 3: weekly; 4: daily or almost daily.

4.1. Strengths and limitations

One of the strengths of this study is that it uses both survey and register-based data. General-population-based survey measures of alcohol use are apt because they contain information on level and pattern of drinking. Another advantage of survey data is that the alcohol use measure does not require a treatment episode or other severe event, such as an arrest or health-related harm, in order to be recorded; therefore, surveys are able to capture sub-clinical problematic drinking (Brummer et al., 2021). Thus, the present study had the benefit of being able to detect individuals with hazardous drinking that is evident in survey responses but which may not be so severe that such individuals appear in administrative datasets (Haeny et al., 2018). Register data have the advantage of near full population coverage over long periods (Thygesen and Ersbøll, 2014). Combining survey-based measures of alcohol exposure and register-based outcomes reduces bias due to common methods variance (Podsakoff et al., 2003), since the observed covariation between exposure and outcome is not attributed to the same method being used to measure both variables.

However, there are several limitations of the current study which should be considered. First, because hospital registers likely only identify the most severe instances of violence (Kruse et al., 2010), many incidents may not be captured in this study. Second, our choice of follow-up time was largely practical, as this was the longest period for which hospital data were available. Since the outcome was quite rare, we determined that this eight-year period would be sufficient to conduct meaningful analyses. However, it would be worthwhile to investigate this relationship between drinking and hospitalization for violence in future studies that include a longer follow-up period, as well as in studies with a larger number of participants that could assess a shorter follow-up period to identify more proximal relationships.

A third limitation is that the singular exposure measurement and long follow-up period present some challenges for establishing a causal link between hazardous drinking and violence victimization. When alcohol is investigated for its role in risk of violence victimization and injuries more generally, it typically is operationalized as either an acute or chronic exposure (Taylor et al., 2010; Vinson et al., 2003). Acute exposure refers to drinking that directly precedes the victimization. One interpretation of the relationship between drinking and violence victimization is that intoxication alters an individual's behavior in ways that may increase the risk for victimization. Intoxicated persons may be perceived as "easy targets," viewed as irritating or offensive to others, or be less able to read and impart cues during interactions (MacCoun et al., 2003). In the present study, however, we had no information on the respondent's alcohol use at the time of the violent event resulting in hospital admission. Further, we used an indicator of hazardous drinking drawn from self-reported behavior over a one-year period. It may be that this represents a chronic, relatively stable exposure and that similar drinking habits persisted over the eight-year follow-up period. The evidence on stability of drinking behaviors is mixed, though, and depends on length of time considered, the particular drinking indicator, and the specific subgroup, based on age group, gender, and baseline drinking status (Kerr et al., 2002; Knott et al., 2018). Our ability either to establish hazardous drinking status as a stable exposure or to link our indicator of hazardous drinking and hospitalizations more proximally would be enhanced had we been able to include repeated exposure measures for our cohort or results of blood alcohol concentration analysis at the time of the hospital admission.

There are other possible explanations for an observed relationship between hazardous drinking and violence victimization beyond the psychopharmacological effects of intoxication. There may be some factors that underlie both alcohol consumption and violent victimization, such as poor impulse control. Furthermore, those with chronic hazardous drinking patterns may spend more time in high-risk drinking environments, like bars and nightclubs, and may have more contact with individuals who are at higher risk of perpetrating violence. This type of explanation falls under the category of lifestyle theories of victimization and emphasizes that engaging in certain behaviors increases one's exposure to risky times, places and people, which, in turn, increases the probability of experiencing victimization (Pratt and Turanovic, 2016). However, while such factors may be confounders, there is also the possibility that they mediate the relationship between drinking and victimization (Taylor et al., 2010). For instance, in the case of low self-control, it could be that hazardous drinking increases impulsivity, which then increases the risk of victimization (Turanovic et al., 2015).

5. Conclusions

We found that hazardous drinking is associated with future hospitalizations for violence among the general population in Denmark and that gender moderates the effect of an increasing AUDIT-C score on victimization. By linking survey data on alcohol use and administrative data on hospital admissions for violence, this study applies a novel approach and contributes to the diverse and growing body of evidence on the relationship between hazardous drinking and risk of violence victimization. Future research could examine more closely the direct psychopharmacological effects of alcohol, consider unmeasured confounders, as well as the causal pathways through which heavy drinking indirectly increases the risk of violence victimization.

Role of Funding Source

The study was funded by intramural sources from the Centre for Alcohol and Drug Research and an unrestricted grant for a doctoral scholarship from the School of Business and Social Sciences at Aarhus University (JB). The funders had no say in the decision to publish or influence on the content of the manuscript.

CRediT authorship contribution statement

Julie Brummer: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing, Visualization. Kim Bloomfield: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing. Katherine J. Karriker-Jaffe: Conceptualization, Writing – review & editing, Supervision. Morten Hesse: Conceptualization, Writing – review & editing, Formal analysis, Methodology, Supervision, Writing – review & editing, Visualization.

Declarations of Interest

The authors confirm that this work is original and has not been previously published, nor is it under consideration for publication elsewhere. Each author has made a significant contribution to the work, and all approve of the attached manuscript. The authors have no conflicts of interest to disclose.

Acknowledgments

We would like to thank Ulrike Grittner of the Institute of Biometry and Clinical Epidemiology, Charité– Universitätsmedizin Berlin for providing statistical advice.

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DOI: 10.1111/add.16034

RESEARCH REPORT

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Using the alcohol use disorders identification test to predict hospital admission for alcohol-related conditions in the Danish general population: a record-linkage study

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Abstract

Background and Aims: Most studies validating the alcohol use disorders identification test (AUDIT) have either assessed its factor structure and/or test-retest reliability or used diagnostic interviews as validators of current alcohol use disorders. The aim of the present study was to determine whether AUDIT and AUDIT-Consumption (AUDIT-C) scores are associated with subsequent risk of hospital admission for alcohol-related disorders and diseases (ARDDs).

Design: We used a historical cohort study. Using national registers, survey respondents were tracked from 1 September 2011 to hospitalization for an ARDD, emigration, death, or 31 December 2018, whichever occurred first.

Setting: Denmark.

Participants: Respondents (n = 4522) from a Danish national survey conducted in autumn 2011.

Measurements: Outcome was incident ARDD admission recorded in the National Patient Register. Predictors were AUDIT and AUDIT-C scores, and covariates were age, gender, highest level of education and previous psychiatric disorder.

Findings: During the study period, 56 respondents had a first-time ARDD admission. Respondents who scored above the 8-point AUDIT cut-off and respondents who scored above the 5-point AUDIT-C cut-off had a significantly increased risk of being admitted for an ARDD compared with respondents who scored below the cut-offs, (AUDIT: hazard ratio (HR), 4.72; 95% CI, 2.59–8.60; AUDIT-C: HR, 7.97; 95% CI, 3.66–17.31).

Conclusions: Scores above alcohol use disorders identification test (AUDIT) and AUDIT-Consumption (AUDIT-C) cut-offs are associated with an increased risk of long-term alcohol-related hospital admissions. At widely used cut-offs, the AUDIT-C is a better predictor of alcohol-related hospitalizations among members of the general population than the full AUDIT.

KEYWORDS

Alcohol, AUDIT, AUDIT-C, cohort, hospitalization, registries, screening, validation

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INTRODUCTION

The 10-question alcohol use disorders identification test (AUDIT) developed by the World Health Organization [1] is a widely-endorsed tool designed to detect hazardous and harmful alcohol use [2-4]. It was initially intended for primary care settings and has been promoted as a means of identifying who may benefit from brief alcohol intervention [4]. Its use subsequently has been extended to other contexts, such as prisons [5], hospitals [6] and research settings [7, 8]. Furthermore, it is often included in general population surveys of drinking practices [9]. Despite the AUDIT's simplicity and relative brevity, the 10-item screening tool may still be too burdensome to be adopted in some settings, for instance, in general practice or emergency departments [10, 11]. The AUDIT-Consumption (AUDIT-C), which comprises the first three items of the full AUDIT, was developed to address such practical concerns and in light of findings showing the importance of frequency of heavy drinking episodes for identifying alcohol problems [10].

Since the publication of the first AUDIT manual, a large number of AUDIT and AUDIT-C validation studies have been carried out to assess the tool's performance in different countries [12–15] and populations, such as university students [16], recently released prisoners [17] and general population samples [18]. Validation studies have often focused on factor structure [19–22], with some studies supporting the original three-factor structure outlined by the AUDIT developers [15, 23], whereas other studies have found that two-factor (e.g. alcohol consumption and drinking problems) [19, 20, 24] or a single-factor solution [21, 25] provided the best fit. Studies of the psychometric properties of the AUDIT and AUDIT-C administered in various populations have demonstrated that the tools have good test-retest reliability [26–28] and have performed satisfactorily when diagnostic interviews have been used as validators of current alcohol abuse and dependence disorders [29–31].

Beyond assessment of structure and correspondence with other measures of alcohol use disorders, another important consideration for an instrument such as the AUDIT is its ability to predict meaningful real-world outcomes. An early longitudinal study showed that the AUDIT, at a cut-off of eight, was a predictor of self-reported social and medical problems and hospital admissions in the following 2 to 3 years [32] and that the AUDIT's predictive capacity was comparable or superior to laboratory measures. Subsequent research has shown an association between AUDIT and AUDIT-C scores and risk of later health conditions, such as alcohol-related gastrointestinal conditions among veterans [33, 34]. In terms of future drinking behaviours, studies have also found that AUDIT and AUDIT-C scores predict later problematic alcohol use [35] among young people using cut-offs of five and three, respectively. Although longitudinal studies such as these have been carried out, most have not included outcomes likely to pick up the broadest range of directly attributable conditions known to be sequelae of heavy drinking.

Despite considerable work, there is surprisingly little research that answers this central question: is the AUDIT or the AUDIT-C able to indicate if a member of the general population, as assessed, for ADDICTION

example, in a country's health status survey, is at increased risk of developing an alcohol-related disorder or disease (ARDD) leading to hospitalization? The aim of the present study was to assess whether high AUDIT and AUDIT-C scores are associated with risk for future hospital admissions for ARDD in a general population sample over a 7-year follow-up period. The study links AUDIT and AUDIT-C scores taken from a national survey with longitudinal hospital data on ARDDs. It adds to the existing literature by addressing a broad range of hospital-related health conditions over a long observation time.

METHODS

Study design and population

Participants in the present study consisted of respondents to the 2011 Danish National Alcohol and Drug Survey. Using linked hospital register data, this cohort was followed retrospectively from 1 September 2011 until 31 December 2018.

The 2011 national survey was completed online (68%) or via a telephone interview (32%) and was carried out by Statistics Denmark on behalf of the Centre for Alcohol and Drug Research, Aarhus University in September and October 2011 [36]. A random sample of 8004 individuals (ages 15–79) from the Danish civil registration system received a mailed invitation, and 5133 (64%) participated in the survey. The cohort in the present study consists of the 4522 respondents who were not lifetime abstainers, provided information for all AUDIT items and had no previous history of hospitalization related to





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alcohol (Fig. 1). Lifetime abstainers were defined as those respondents who replied, 'No' to the survey question 'Have you ever drunk alcohol?' None of the respondents who reported that they were lifetime abstainers had a history of hospitalizations related to alcohol. In this study, the population was restricted to those of Danish origin to ensure complete medical histories were available, because immigrants and their descendants are more likely to have spent prolonged periods outside of Denmark, and, therefore, their full medical histories would not be reflected in the Danish registers.

Each person who legally resides in Denmark is assigned a personal identification number, and this number can be used to link information in different registers [37] and to link survey and register data. In the present study, data from the 2011 survey were linked with longitudinal hospital records (2011-2018) contained in the Danish National Patient Registry (NPR) [38] to identify hospital-based diagnoses and dates of admission. Additionally, the causes-of-death register and changes of residence register were used to identify date of death and date of emigration from Denmark, respectively. The emigration date was assigned as the date of departure from the last recorded residential address in Denmark.

The study was registered with the Danish Data Protection Agency. Respondents indicated their consent to participate in the survey study by completing the questionnaire. Danish register data are collected and stored for monitoring and quality assurance purposes, and, according to Danish law, no ethics evaluation or informed consent is needed for use of register data. The survey and register data are stored on secure servers at Statistics Denmark.

Measures

AUDIT

The 10 AUDIT questions were included in the 2011 survey. We applied a method of recoding Danish survey national data, described in this section and Supporting information Table S1, which has been used in previous studies to generate AUDIT scores [39].

The 2011 survey assessed past-year use of alcoholic beverages, and participants who responded that they had not consumed alcohol in the past year were not asked further questions about their frequency of use, patterns of drinking or alcohol-related problems. In the present study, these individuals were given a total AUDIT score of zero.

The AUDIT is designed such that respondents score between 0 and 4 points for each item, giving a total minimum score of 0 and a maximum score of 40 [1]. The AUDIT-C consists of the first three AUDIT questions and is scored on a scale of 0 to 12 points [10]. AUDIT items 1 to 8 offer five response options, and items 9 and 10 offer three response options. As detailed in Supporting information Table S1, survey responses were recoded to correspond to the options provided for AUDIT items 1 to 3. AUDIT items 4 to 10 were presented consecutively in the survey. For items 4 to 6, separate survey response options for 'Daily' and 'Almost daily' were collapsed to correspond to the AUDIT option 'Daily or almost daily'. For question 10, the survey response options were 'No', 'Yes, once' and 'Yes, more than once'. Otherwise, these questions and responses replicated the AUDIT instrument.

Register data on hospital admissions for ARDD

ARDDs were identified through data linkage with the Danish NPR [38]. The NPR contains individual-level administrative and diagnostic hospital data for the Danish population and is updated regularly. The NPR has been active since 1977, and, in 1995, was expanded to contain information from emergency departments, psychiatric departments and outpatient clinics [40]. As of 1994, the NPR has used International Classification of Diseases (ICD-10) codes to specify the primary reason for the hospital contact, and, when relevant, supplemental, secondary diagnoses [38]. In the present study, ARDDs were identified using ICD-10 diagnoses codes recommended for Swedish register studies [41] and found in the NPR [42] (Supporting information Table S2).

Date of hospital admission was used to determine if an ARDD diagnosis occurred before or subsequent to the survey. An incident ARDD diagnosis was defined as one that occurred after 1 September 2011 (i.e. following the administration of the survey). A prior ARDD diagnosis was one that occurred between 1 January 1994, when ICD-10 codes were implemented, and 31 August 2011. As the analyses were carried out to assess time to incident admission after the survey, only participants without prior admission for an ARDD were included.

Additional covariates

Our study included the following covariates: age, gender, highest level of education and prior psychiatric disorder. Age was included as a continuous variable, separated in decades, in the regression analysis and as a categorical variable with four groups in the descriptive analysis. Gender was coded as male or female based on the participant's survey response. The participant's highest level of education achieved at baseline was identified using responses to the 2011 survey and was classified in three categories: low (compulsory education or less), medium (vocational or upper secondary education) and high (higher education). A respondent was considered to have a prior psychiatric disorder if they had an F2 (schizophrenia, schizotypal and delusional), F3 (mood), F4 (neurotic, stress-related and somatoform) or F6 (adult personality and behaviour) ICD-10 diagnosis in the NPR before 1 September 2011.

Statistical analyses

Participants were dichotomized twice into subgroups based on a cut-off point of eight [1] for the full AUDIT and another cut-off point
of five for the AUDIT-C [43]. The AUDIT cut-off was selected because it is recommended by the developers of the tool and is widely used [1], whereas, for the AUDIT-C, because there is not a comparable standard cut-off, the cut-off established in a general population of Germany, a neighbouring country, was used [43]. To provide an overview of the study sample, and to compare respondents who scored above and below the AUDIT and AUDIT-C cut-offs in terms of the other covariates, cross-tabulations with corrected, weighted χ^2 tests were used.

Participants were followed using Danish register data from 1 September 2011 until first hospitalization for an ARDD, emigration, death or end of the study on 31 December 2018, whichever occurred first. Crude, weighted incidence rates (IRs) for ARDD were calculated with jack-knife 95% CIs for the total study population and by AUDIT and AUDIT-C status. To further examine the relationship between AUDIT and AUDIT-C scores and time to first hospital admission for an ARDD, cumulative hazard curves were generated, and a Cox proportional hazard model was used to calculate hazard ratios (HRs) with 95% CIs. The proportional hazards assumption was assessed graphically through a visual inspection of a log–log plot and then tested using Schoenfeld residuals. Neither method indicated nonproportional hazards.

As a sensitivity analysis, alternate cut-off points were assessed. Receiver operating characteristic curves (ROC) were generated, with ARDD as the gold standard. The optimal AUDIT and AUDIT-C cutoffs for the population were identified using the Youden Index, which takes into account sensitivity and specificity [44]. These alternate cut-off points were then applied in a Cox proportional hazard model to assess the robustness of the original findings.

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Weights created by Statistics Denmark to reflect the age, gender, family structure, education, income and country of origin of the national population were used in the analyses, unless noted. All analyses were carried out using STATA v.16 [45] or R [46]. Because the analysis plan was not pre-registered, the reported findings should be considered exploratory.

RESULTS

Description of participants, outcomes and AUDIT

The proportion of participants who scored above the AUDIT cut-off (\geq 8) was 28.8%. Most respondents (55%) acquired all points from the first three items of the AUDIT (i.e. the AUDIT-C).

The prevalence of an AUDIT score above the cut-off was higher among men (38.0%) than women (19.4%). Higher proportions with AUDIT scores above the cut-off were also found among the youngest age group and those with the lowest level of education. Similar results were observed regarding AUDIT-C scores in terms of gender and age; however, differences in AUDIT-C status among participants of varying levels of education were not statistically significant (Table 1).

| | Overall, n | AUDIT <8, weighted % | AUDIT ≥8, weighted % | Р | AUDIT-C <5, weighted % | AUDIT-C ≥5, weighted % | Р |
|---|------------|-------------------------|-------------------------|--------|---------------------------|---------------------------|--------|
| Total | 4522 | 71.22 | 28.78 | | 53.00 | 47.00 | |
| Gender | | | | <0.001 | | | <0.001 |
| Male | 2145 | 61.99 | 38.01 | | 40.72 | 59.28 | |
| Female | 2377 | 80.57 | 19.43 | | 65.46 | 34.54 | |
| Age group (y) | | | | <0.001 | | | <0.001 |
| 15-29 | 952 | 40.38 | 59.62 | | 27.69 | 72.31 | |
| 30-45 | 1144 | 74.39 | 25.61 | | 59.55 | 40.45 | |
| 46-64 | 1654 | 80.09 | 19.91 | | 57.64 | 42.36 | |
| 65+ | 772 | 88.61 | 11.39 | | 66.45 | 33.55 | |
| Highest level of education ^{a,b} | | | | 0.021 | | | 0.054 |
| Low | 952 | 69.21 | 30.79 | | 51.83 | 48.17 | |
| Medium | 2063 | 70.29 | 29.71 | | 51.72 | 48.28 | |
| High | 1423 | 74.26 | 25.74 | | 55.96 | 44.04 | |
| Prior psychiatric disorder | | | | 0.391 | | | 0.223 |
| No | 4325 | 71.37 | 28.63 | | 52.77 | 47.23 | |
| Yes | 197 | 68.37 | 31.63 | | 57.39 | 42.61 | |

TABLE 1 Study population characteristics by drinking status (*n* = 4522).

Abbreviations: AUDIT, alcohol use disorders identification test; AUDIT-C, alcohol use disorders identification test-consumption. ^aMissing data for 84 respondents.

^bLow = compulsory education; Medium = upper secondary education or vocational training, High = higher education.

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AUDIT and ARDDs

Participants contributed a total of 32 288.33 follow-up person-years, with those with high AUDIT scores contributing 8922.18 person-years, and those with low AUDIT scores contributing 23 366.15 person-years. Of a total of 56 admissions for ARDDs, 35 occurred in the high AUDIT group and 21 in the low AUDIT group. The weighted IRs among those with high and low AUDIT scores were 441.32 (95% CI, 315.77-636.24) and 109.81 (95% CI, 71.15-178.88)

AUDIT-C and ARDDs

Those with high AUDIT-C scores contributed 14 924.44 person-years and had 48 admissions for ARDDs, and those with low AUDIT-C scores contributed 17 636.89 person-years and had eight admissions for ARDDs. The weighted IRs among those with high and low AUDIT-C scores were 380.88 (95% CI, 285.84–519.17) and 49.86 (95% CI, 24.77–116.26) per 100 000 person-years, respectively (Table 2). Cumulative hazard by AUDIT-C score is shown in Fig. 2, left panel.

TABLE 2 Descriptive overview of first hospital admissions for ARDD according to AUDIT and AUDIT-C status, 2011 to 2018 (n = 4522) (unadjusted).

| | AUDIT <8 (n = 3270) | AUDIT ≥8 (n = 1252) | Total (n = 4522) |
|---|-----------------------|------------------------|------------------------|
| No. of first admissions (unweighted) | 21 | 35 | 56 |
| Follow-up years (unweighted) | 23 366.15 | 8922.18 | 32 288.33 |
| Weighted incidence rate/100 000 person-years | 109.81 (71.15-178.88) | 441.32 (315.77-636.24) | 205.25 (157.22-273.26) |
| | AUDIT-C <5 (n = 2428) | AUDIT-C ≥5 (n = 2094) | |
| No. of first admissions (unweighted) | 8 | 48 | 56 |
| Follow-up years (unweighted) | 17 636.89 | 14 924.44 | 32 288.33 |
| Weighted incidence rate/100 000 person-years (95% CI) | 49.86 (24.77-116.26) | 380.88 (285.84-519.17) | 205.25 (157.22-273.26) |

Abbreviations: ARDD, alcohol-related disorder or disease; AUDIT, alcohol use disorders identification test; AUDIT-C, alcohol use disorders identification test-consumption.



FIGURE 2 Cumulative hazard and 95% confidence bands for alcohol-related disorder or disease (ARDD) by alcohol use disorders identification test-consumption (AUDIT-C) or full AUDIT cut-off

Multivariable analyses of AUDIT and AUDIT-C scores and hospitalizations for ARDDs

Table 3 shows that participants who scored above the AUDIT cut-off (adjusted model 1) had a significantly increased risk of being hospitalized for an ARDD compared to participants who scored below the AUDIT cut-off (HR, 4.72; 95% CI, 2.59–8.60). An AUDIT-C score above the cut-off (adjusted model 2) was also associated with increased risk of hospitalization for an ARDD (HR, 7.97; 95% CI, 3.66–17.31). In addition, in both models, a significantly increased risk of hospitalization was observed among participants without higher education, older participants and participants with a history of psychiatric disorders.

Sensitivity analyses

Results of the ROC, based on Youden's index, indicate that the optimal cut-off for this sample is seven for the AUDIT and six for the AUDIT-C (Supporting information Table S3). When these cut-offs were applied in the multivariable survival analyses, scores above the cut-offs for both tools were associated with an increased risk of ARDD hospitalization, with a stronger association remaining for the AUDIT-C (AUDIT: HR, 5.86; 95% CI, 3.09–11.11; AUDIT-C: HR, 6.98; 95% CI, 3.69–13.18) (Supporting information Table S4). The area

under the ROC curve was comparable for the AUDIT (0.7423) and the AUDIT-C (0.7498) and in the acceptable range [47].

DISCUSSION

Both the AUDIT and the AUDIT-C were robustly associated with ARDD hospitalizations. Therefore, in terms of this important realworld outcome, self-reported survey data was able to discriminate well between people who would later be hospitalized because of drinking and those who would not. In the context of this study, which involved a general population sample with a high proportion of heavy drinkers, the AUDIT-C was more strongly associated with future alcohol-related outcomes than the full AUDIT at the cut-offs of eight for the AUDIT and five for the AUDIT-C. This finding was replicated when alternate cut-offs were assessed based on results of ROC analyses. Although the findings should be seen in light of the small number of events overall in this study, they are nevertheless a point in support of the view that the brief AUDIT-C is potentially as informative as the full instrument in predicting long-term drinking outcomes.

Furthermore, the results offer support for prioritizing the threequestion tool in settings where time is limited, such as emergency departments [11, 48]. In this sample, more than half of participants did not earn any points from the last seven questions of the AUDIT.

TABLE 3 Crude and adjusted HRs and 95% Cls from Cox proportional hazards models examining relationship between variables and time to first hospital admission for ARDD (weighted; *n* = 4522).

| | Unadjusted regressions | | Adjusted model 1 | | Adjusted model 2 | |
|---------------------------------|------------------------|--------|-----------------------------------|--------|-----------------------------------|--------|
| Variable | Unadjusted HR (95% CI) | Р | Adjusted HR (95% CI) ^b | Р | Adjusted HR (95% CI) ^c | Р |
| Drinking status | | | | | | |
| AUDIT score <8 | 1 (ref) | | 1 (ref) | | | |
| AUDIT score ≥8 | 4.01 (2.28-7.06) | <0.001 | 4.72 (2.59-8.60) | <0.001 | | |
| AUDIT-C score <5 | 1 (ref) | | | | 1 (ref) | |
| AUDIT-C score ≥5 | 7.63 (3.52-16.57) | <0.001 | | | 7.97 (3.66-17.31) | <0.001 |
| Gender | | | | | | |
| Male | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Female | 0.51 (0.29-0.89) | 0.019 | 0.61 (0.34-1.09) | 0.098 | 0.70 (0.39-1.25) | 0.225 |
| Age (decades) | 1.05 (0.90-1.23) | 0.539 | 1.27 (1.09–1.47) | 0.002 | 1.20 (1.04–1.37) | 0.010 |
| Level of education ^a | | | | | | |
| High | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Medium | 1.48 (0.70-3.10) | 0.303 | 1.41 (0.67–2.95) | 0.367 | 1.41 (0.67–2.99) | 0.366 |
| Low | 3.20 (1.50-6.79) | 0.003 | 3.01 (1.44-6.26) | 0.003 | 3.06 (1.47-6.37) | 0.003 |
| Prior psychiatric disorder | | | | | | |
| No | 1 (ref) | | 1 (ref) | | 1 (ref) | |
| Yes | 3.50 (1.61-7.59) | 0.002 | 3.07 (1.31-7.20) | 0.010 | 3.34 (1.41-7.86) | 0.006 |

Abbreviations: ARDD, alcohol-related disorder or disease; AUDIT, alcohol use disorders identification test; AUDIT-C = alcohol use disorders identification test-consumption; CI, confidence interval; HR, hazard ratio.

^aHigh = higher education; Medium = upper secondary education or vocational training; Low = compulsory education.

^bModel 1 includes AUDIT cut-off, gender, age, highest level of education and prior psychiatric disorder.

^cModel 2 includes AUDIT-C cut-off, gender, age, highest level of education and prior psychiatric disorder.

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This is consistent with the observation of the AUDIT developers, who noted that among those categorized as hazardous drinkers by the AUDIT, most acquire the majority of their points from AUDIT-C items [1]. The performance of the AUDIT-C in this study indicates that consumption and specifically high-volume drinking, which the AUDIT-C has been shown to be superior at detecting [10, 49], is a crucial indicator of future ARDD hospitalization and is in line with the argument that heavy use is the key marker of alcohol use disorders [50]. In the present study, the additional questions that cover the AUDIT developer's proposed 'conceptual domains' of 'alcohol dependence' and 'adverse consequences of drinking' [1] did not improve the predictive capacity of the screening tool. Such items may be relevant to predict other outcomes or for a clinical population; however, in terms of alcohol-related hospitalizations for the drinker, the last seven items of the AUDIT do not seem to add relevant predictive information for a general population sample.

Strengths and limitations

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As different data sources were used for the exposure and outcome variables, the risk of bias because of common methods variance was minimized. In contrast, in validation studies where self-reports are used as the sole measurement source, common methods bias can stem from common rater effects such as consistency motif and social desirability [51, 52], and some of the observed covariation may be because of the fact that participants' responses reflect their desire to answer consistently or to portray themselves favourably [51, 52]. By using an outcome measure that is not dependent on informant reports, the relationship between AUDIT/AUDIT-C scores and hospitalizations for ARDD observed in the present study cannot be attributed to the use of a common measurement method.

A further strength is that we defined our outcome to capture the full range of ARDDs. The outcome measure was drawn from national registers with good coverage, and it is unlikely that a large number of people without alcohol problems will be hospitalized for alcoholrelated disorders, reducing the risk of false positives.

However, some limitations must also be acknowledged. The outcome event in our study is rare, making precise estimation difficult and is likely to represent only the 'tip of the iceberg' in terms of alcohol problems at the population level. Many people with serious alcohol problems may not develop conditions that are fully attributable to drinking, but rather experience outcomes, such as cancers, heart conditions or injuries that are more indirectly associated with or partially attributable to drinking [53, 54].

Furthermore, although the survey used in this study included all items covered by the AUDIT, survey response options were recoded to fit the corresponding AUDIT response categories, as is common when the AUDIT is embedded in larger national surveys (e.g. Dawson *et al.* and O'Brien *et al.*) [48, 55], resulting in a version of the AUDIT/AUDIT-C that is slightly different from the versions used in other contexts. By incorporating beverage-specific survey questions

to determine responses to the first three AUDIT items, the present study likely yielded higher consumption estimates and therefore, identified more hazardous drinkers [56, 57] than the original versions of the AUDIT and AUDIT-C would have using the same cut-off points.

As well, it should be acknowledged that the results may have differed had other cut-offs been assessed. Different optimal cut-offs have been demonstrated by prior studies in other countries [58] and subpopulations [59]. However, the main analyses in the present study assessed commonly applied cut-offs, because there is value in evaluating whether such cut-offs do in fact predict important alcohol-related outcomes, and there is also a significant advantage to maintaining consistency in AUDIT/AUDIT-C studies if the tools are to be accepted and applied in clinical settings.

CONCLUSIONS

The present study contributes to the AUDIT and AUDIT-C validation literature with findings showing that both AUDIT and AUDIT-C scores are associated with severe, real-world consequences. Hospital admission for ARDD is a meaningful outcome both because it reflects a serious consequence of hazardous drinking for the individual and in terms of significant economic costs for society [60]. A score above the cut-off on the three-question screening tool AUDIT-C was strongly associated with future hospitalization for ARDD, and adding the additional seven questions of the full AUDIT did not substantially contribute more information. Therefore, in cases where brevity of data collection is crucial, in either clinical settings or general population health surveys, the AUDIT-C presents itself as another valid and brief screening tool.

Register-based AUDIT validation studies could be extended using non-hospital medical registers. For instance, in Finland, International Classification of Primary Care codes are used to classify presenting problems and diagnoses related to healthcare visits to general practice [61], including short-term and long-term alcohol misuse [61]. Finnish healthcare registers also include information on procedures and interventions delivered as part of primary healthcare (e.g. substanceabuse-related guidance and outpatient detoxification) [61]. This type of register data on primary care contacts is not available in Denmark; however, future research in other Nordic countries could involve assessing the predictive validity of the AUDIT in terms of general practice diagnosis related to drinking and comparing such results to the prediction of hospital-based ARDD.

ACKNOWLEDGEMENTS

The study was funded by intramural sources from the Centre for Alcohol and Drug Research and an unrestricted grant for a doctoral scholarship from the School of Business and Social Sciences at Aarhus University (JB).

DECLARATION OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Julie Brummer: Conceptualization; data curation; formal analysis; methodology; visualization. Kim Bloomfield: Conceptualization; funding acquisition; investigation; project administration; resources; supervision. Katherine J Karriker-Jaffe: Conceptualization; supervision. Michael Mulbjerg Pedersen: Conceptualization; formal analysis; methodology; visualization. Morten Hesse: Conceptualization; data curation; formal analysis; methodology; supervision; visualization.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Brummer J, Bloomfield K, Karriker-Jaffe KJ, Pedersen MM, Hesse M. Using the alcohol use disorders identification test to predict hospital admission for alcohol-related conditions in the Danish general population: a record-linkage study. Addiction. 2023;118(1):86–94. <u>https://</u> doi.org/10.1111/add.16034



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Declaration of co-authorship*

Full name of the PhD student: Julie Elizabeth Brummer

This declaration concerns the following article/manuscript:

| Title: | How do register-based studies contribute to our understanding of alcohol's |
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| | harms to family members? A scoping review of relevant literature |
| Authors: | Julie Brummer, M.P.H, Morten Hesse, Ph.D., Kirsten Søndergaard Frederiksen, |
| | M.A., Katherine J. Karriker-Jaffe, Ph.D., Kim Bloomfield, Dr.P.H. |

The article/manuscript is: Published \Box Accepted \boxtimes Submitted \Box In preparation \Box

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| 2. Planning of the experiments/methodology design and development | Α |
| 3. Involvement in the experimental work/clinical studies/data collection | Α |
| 4. Interpretation of the results | В |
| 5. Writing of the first draft of the manuscript | Α |
| 6. Finalization of the manuscript and submission | A |

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| Title: | Hazardous drinking and violence-related hospitalizations in the Danish general | | |
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If published, state full reference: Brummer, J., Bloomfield, K., Karriker-Jaffe, K.J., Hesse, M., 2022. Hazardous drinking and violence-related hospitalizations in the Danish general population: A historical cohort study. *Drug and Alcohol Dependence* 233, https://doi.org/10.1016/j.drugalcdep.2022.109338.

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- D. Minor contribution
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| Element | Extent (A-E) |
|--|--------------|
| 1. Formulation/identification of the scientific problem | В |
| 2. Planning of the experiments/methodology design and development | В |
| 3. Involvement in the experimental work/clinical studies/data collection | E |
| 4. Interpretation of the results | Α |
| 5. Writing of the first draft of the manuscript | Α |
| 6. Finalization of the manuscript and submission | Α |

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