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Alcohol consumption, motivation to change drinking behaviour, motivation to seek help for alcohol problem drinking and alcohol-attributable morbidity

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LIST OF ABBREVIATIONS

AAF	Alcohol-attributable fraction
ALT	Alanine aminotransferase
BMA	British Medical Association
BMI	Body mass index
CI	Confidence Interval
FLD	Fatty liver disease
ICD	International Classification of Diseases
M-CIDI	Münchener Composite International Diagnostic Interview
OR	Odds Ratio
RCQ	Readiness to Change Questionnaire
SHIP	Study of Health in Pomerania
TReaT	Treatment Readiness Tool
TTM	Trans-Theoretical Model of Behaviour Change

SUMMARY

Background: Alcohol consumption accounts for a high burden of disease. The general population of West Pomerania has been characterized as a population at risk with a high prevalence of behavioural risk factors such as alcohol risk drinking. This is reflected by the high proportion of patients being admitted to general hospitals due to alcohol-attributable diseases. The aims of the present dissertation were (a) to analyze dose-response relations between volume of alcohol drinking and the risk of diseases with different alcohol-attributable fractions (AAF) in general hospital inpatients (study 1); (b) to assess motivation to change drinking behaviour and motivation to seek help for alcohol problems during their hospital stay as well as changes in motivation to change drinking behaviour, motivation to seek help and changes in daily alcohol consumption across time according to diseases with different AAFs (study 2); and (c) to investigate the association of fatty liver disease (FLD) with blood pressure and hypertension in a general population sample and to test for the specific contribution of alcohol consumption to this association (study 3).

Methods: For studies 1 and 2, data from 'Early Intervention at General Hospitals', a randomized controlled trial to test the effectiveness of brief intervention for alcohol problem drinking in general hospitals, were used. Study 1 comprised data from 846 inpatients, study 2 comprised data from 294 inpatients aged 18 to 64 years with alcohol problem drinking and alcohol-attributable diseases from four general hospitals in West Pomerania. Hospital diagnoses were classified according to their AAF: (1) diseases wholly attributable to alcohol consumption by definition (AAF=1), (2) diseases partially attributable to alcohol consumption (AAF<1), and (3) diseases with no relation to alcohol consumption or where alcohol consumption has been found to be a protective factor (AAF=0). Study 3 encompassed data from the 'Study of Health in Pomerania', a general population sample of 3191 adults aged 20-79 years. FLD was defined using ultrasound in combination with increased serum alanine aminotransferase levels.

Results: Analyses showed that 46.8% of the general hospital inpatients had a disease attributable to alcohol consumption. There was a dose-response relationship between volume of alcohol drinking and the risk of diseases with different AAFs. Inpatients consuming >120 g and inpatients consuming 61-120 g of pure alcohol per day revealed significantly higher odds for diseases with AAF=1 compared to inpatients consuming 31-60 g of pure alcohol per day with odds ratios (OR) of 6.3 (95% CI 3.6-11.3) and 2.9 (95% CI 1.6-5.1), respectively. Regarding diseases with AAF<1, inpatients consuming >120 g of pure alcohol per day had

significantly higher odds compared to inpatients consuming 31-60 g of pure alcohol per day (OR 2.0, CI 1.2-3.4).

Analyses on motivation to change drinking behaviour and on motivation to seek help at hospitalization revealed that motivation to change drinking behaviour was higher among inpatients with alcohol-attributable diseases than among inpatients without alcohol-attributable diseases ($p<.001$). Among inpatients with AAF=1, motivation to seek help was higher than among inpatients with AAF<1 and AAF=0 ($p<.001$). While motivation to change drinking behaviour remained stable within one year after hospitalization in all three AAF groups, motivation to seek help decreased in this time period. The volume of alcohol consumed decreased in all three AAF groups within one year after hospitalization.

Data from the general population study revealed that FLD was associated with blood pressure and hypertension at baseline and at five-year examination follow-up. For example, the chance of hypertension at both time points was threefold higher in individuals with FLD (OR 2.8, CI 1.3-6.2; OR 3.1, CI 1.7-5.8, respectively) compared to individuals without FLD. Analyses further revealed that the association of FLD with blood pressure and hypertension was independent of alcohol consumption.

Conclusion: The results of the present dissertation provide relevant implications for public health. In view of the high proportion of general hospital inpatients with alcohol-attributable diseases, a screening procedure for problem drinking is needed. Furthermore, appropriate interventions considering the inpatient's motivational level have to be implemented. The concept of AAFs to classify disease conditions according to their causal relationship with alcohol consumption might be a tool to detect inpatients with problem drinking. The results regarding FLD and its association with blood pressure and hypertension demonstrate that it is important to pay attention to alcohol-attributable diseases in the general population and that alcohol-attributable diseases are associated with subsequent serious sequelae. The results of the present work further indicate that the concept to distinguish between alcoholic and non-alcoholic origin of FLD might be obsolete and should be replaced by a concept that regards FLD as a multifactorial disease condition.

ZUSAMMENFASSUNG

Hintergrund: Alkoholkonsum ist mit einer erheblichen Krankheitslast verbunden. Die Bevölkerung Vorpommerns ist als Risikopopulation charakterisiert, innerhalb derer verhaltensbedingte Risikofaktoren wie riskanter Alkoholkonsum hochprävalent sind. Dies spiegelt sich in der hohen Rate an Patienten wider, die aufgrund alkohol-attributabler Erkrankungen in ein Allgemeinkrankenhaus aufgenommen werden. Die Ziele der vorliegenden Dissertation bestanden darin, a) Dosis-Wirkungs-Beziehungen zwischen Alkoholkonsum und dem Risiko für Erkrankungen mit unterschiedlichen alkohol-attributablen Fraktionen (AAF) in Allgemeinkrankenhauspatienten zu untersuchen (Studie 1); b) die Motivation, das Trinkverhalten zu verändern und die Motivation, Hilfe bei Alkoholproblemen in Anspruch zu nehmen in Abhängigkeit von dem Vorliegen von Erkrankungen mit unterschiedlichen AAF während des Krankenhausaufenthaltes zu analysieren (Studie 2); (c) Veränderungen in Hinblick auf die Motivation sowie den täglichen Alkoholkonsum in Abhängigkeit von dem Vorliegen von Erkrankungen mit unterschiedlichen AAF innerhalb eines Jahres nach dem Krankenhausaufenthalt zu prüfen (Studie 2) und schließlich d) die Assoziation zwischen der Fettlebererkrankung und Blutdruck sowie arterieller Hypertonie in einer Allgemeinbevölkerungsstichprobe zu analysieren sowie den Einfluss des Alkoholkonsums auf diese Assoziation zu untersuchen (Studie 3).

Methoden: Für die Studien 1 und 2 wurden Daten aus der randomisierten Kontrollgruppenstudie "Kurzintervention im Krankenhaus", einem Forschungsprojekt zur Überprüfung der Effektivität einer Kurzintervention bei Krankenhauspatienten mit problematischem Alkoholkonsum, genutzt. Die Stichproben umfassten 846 bzw. 294 Krankenhauspatienten im Alter von 18 bis 64 Jahren mit problematischem Alkoholkonsum und alkohol-attributablen Erkrankungen aus vier Allgemeinkrankenhäusern in Vorpommern. Die Behandlungsdiagnosen wurden anhand ihrer AAF in drei Gruppen unterteilt: (1) Erkrankungen, die vollständig auf Alkoholkonsum zurückzuführen sind (AAF=1); (2) Erkrankungen, zu deren Entstehung Alkoholkonsum einen beitragenden Einfluss hat (AAF<1) und (3) Erkrankungen, die in keinem Zusammenhang mit Alkoholkonsum stehen bzw. für die ein protektiver Effekt des Alkoholkonsums nachgewiesen werden konnte (AAF=0). Die Studie 3 umfasste Daten aus der "Study of Health in Pomerania", einer populationsbasierten Kohortenstudie mit 3191 Erwachsenen im Alter von 20 bis 79 Jahren. Die Definition der Fettlebererkrankung erfolgte auf Basis einer Lebersonographie in Kombination mit erhöhten Werten des Leberenzyms Alanin-Aminotransferase im Serum.

Ergebnisse: Die Analysen ergaben, dass bei 46.8% der untersuchten Krankenhauspatienten eine alkohol-attributable Erkrankung vorlag. Darüber hinaus konnte eine Dosis-Wirkungs-Beziehung zwischen der täglich konsumierten Alkoholmenge und dem Risiko für Erkrankungen mit unterschiedlichen AAF aufgezeigt werden. Patienten mit einem täglichen Konsum von >120 g und 61-120 g Reinalkohol wiesen eine signifikant höhere Wahrscheinlichkeit auf an einer Erkrankung mit AAF=1 zu leiden im Vergleich zu Patienten mit einem täglichen Konsum von 31-60 g Reinalkohol (OR 6.3, CI 3.6-11.3; OR 2.9, CI 1.6-5.1). Bezüglich Erkrankungen mit AAF<1 wiesen Patienten mit einem täglichen Konsum von >120 g Reinalkohol eine signifikant höhere Wahrscheinlichkeit auf als Patienten mit einem täglichen Konsum von 31-60 g Reinalkohol (OR 2.0, CI 1.2-3.4).

Die Analysen zur Motivation, das Trinkverhalten zu verändern und zur Motivation, Hilfe bei Alkoholproblemen in Anspruch zu nehmen ergaben, dass die Veränderungsmotivation während des Krankenhausaufenthaltes bei Patienten mit alkohol-attributablen Erkrankungen höher war als bei Patienten ohne alkohol-attributable Erkrankungen ($p<.001$). In der Gruppe der Patienten mit Erkrankungen mit AAF=1 war die Inanspruchnahmemotivation während des Krankenhausaufenthaltes signifikant höher als in der Gruppe der Patienten mit Erkrankungen mit AAF<1 und AAF=0 ($p<.001$). Während die Veränderungsmotivation innerhalb eines Jahres nach dem Krankenhausaufenthalt in allen drei Gruppen konstant blieb, sank die Inanspruchnahmemotivation. Die täglich konsumierte Alkoholmenge sank in allen drei Gruppen innerhalb eines Jahres nach dem Krankenhausaufenthalt.

Die Daten aus der Allgemeinbevölkerungsstudie zeigten eine signifikante Assoziation zwischen der Fettlebererkrankung und Blutdruck sowie arterieller Hypertonie zum Zeitpunkt der Basisuntersuchung sowie nach fünf Jahren. Beispielsweise wiesen Studienteilnehmer mit Fettleberkrankung zu beiden Messzeitpunkten eine dreifach höhere Wahrscheinlichkeit für Hypertonie auf als Studienteilnehmer ohne Fettleberkrankung (OR 2.8, CI 1.3-6.2; OR 3.1, CI 1.7-5.8). Die Analysen zeigten darüber hinaus, dass diese Assoziation unabhängig vom Alkoholkonsum der Studienteilnehmer bestand.

Schlussfolgerung: Die Ergebnisse der vorliegenden Dissertation liefern wichtige Implikationen für die Praxis. In Hinblick auf den hohen Anteil an Krankenhauspatienten mit alkohol-attributablen Erkrankungen besteht die Notwendigkeit, ein Screening bezüglich problematischen Alkoholkonsums zu implementieren. Darüber hinaus sind Interventionen, die auf das Motivationsstadium des Patienten abgestimmt sind, unabdingbar. Das Konzept der AAF stellt eine Möglichkeit dar, Patienten mit problematischem Alkoholkonsum zu detektieren. Die Ergebnisse zur Assoziation zwischen Fettleber und Blutdruck sowie

arterieller Hypertonie zeigen auf, dass alkoholbezogene Erkrankungen auch in der Allgemeinbevölkerung von hoher Bedeutung sind und mit ernstzunehmenden Folgeerkrankungen assoziiert sind. Darüber hinaus liefern die Ergebnisse der vorliegenden Arbeit Hinweise darauf, dass das Konzept der Unterscheidung zwischen alkoholbedingter und nicht-alkoholbedingter Fettlebererkrankung revidiert und durch ein Konzept ersetzt werden sollte, in dem die Fettlebererkrankung als multifaktorielle Erkrankung betrachtet wird.

1. INTRODUCTION

1.1 Alcohol consumption and alcohol-attributable morbidity

Alcohol consumption is one of the most important risk factors for burden of disease and related to more than 60 medical conditions (Rehm et al., 2003). The importance of alcohol consumption as a risk factor for disease is highlighted by the fact that more than 30 three-digit or four-digit codes listed in the International Classification of Diseases (ICD) include alcohol in their name or definition, and more than 200 three-digit ICD-10 codes exist, in which alcohol is part of a component cause (Rehm et al., 2009).

Europe has been reported to have the highest alcohol consumption per capita and the highest alcohol-attributable burden of disease worldwide (Rehm et al., 2006b). In 2002, the average per capita consumption of pure alcohol in the European region was 12.1 litres, on average more than 100% above the global per capita consumption (Rehm et al., 2006b). This results in a considerable disease burden: 6.1% of all deaths were attributable to alcohol consumption (Rehm et al., 2006b).

Although alcohol-attributable mortality is more frequently investigated than alcohol-attributable morbidity, epidemiological evidence for the impact of alcohol consumption on various diseases is given in numerous reviews and meta-analyses investigating dose-response relations between volume of alcohol drinking and the risk of specific alcohol-attributable diseases. Recently, a comprehensive overview on different dimensions of alcohol consumption and burden of disease provided evidence for a causal impact of average volume of alcohol consumption on a broad spectrum of diseases including cancer, liver cirrhosis and pancreatitis. A dose-response relation could be quantified for these disease conditions with the relative risk increasing with drinking volume (Rehm et al., 2010).

Diseases may be classified according to their causal relationship with alcohol consumption using the concept of alcohol-attributable fractions (AAF). AAFs have been defined as the proportion by which disease cases, injury events, or deaths would be reduced if alcohol use and misuse were eliminated among the population (Shultz et al., 1991). Usually, AAFs are derived from meta-analyses or relative risk estimates from cohort studies (Rehm et al., 2009). It is recommended to calculate AAFs for monitoring alcohol use and alcohol-related consequences (Gmel et al., 2009).

Following the approach of Rehm et al. (2006a), diseases may be classified into two groups according to their AAFs: (1) Diseases wholly attributable to alcohol consumption by definition (AAF=1), and (2) diseases partially attributable to alcohol consumption (AAF<1). Diseases with AAF<1 encompass disease conditions where alcohol is a contributory, but not a sufficient cause as malignant neoplasms and hypertension. Disease conditions wholly attributable to alcohol consumption coded according to ICD version 10 are displayed in Table 1.

Table 1 Disease conditions wholly attributable to alcohol consumption according to ICD-10

Condition	ICD-10 code
Alcohol-induced pseudo-Cushing's syndrome	E24.4
Mental and behavioural disorders due to the use of alcohol	F10
Acute intoxication	*F10.0*
Harmful use	*F10.1*
Dependence syndrome	*F10.2*
Withdrawal state	*F10.3*
Withdrawal state with delirium	*F10.4*
Psychotic disorder	*F10.5*
Amnesic syndrome	*F10.6*
Residual and late-onset psychotic disorder	*F10.7*
Other mental and behavioural disorders	*F10.8*
Unspecified mental and behavioural disorder	*F10.9*
Degeneration of nervous system due to alcohol	G31.2
Alcoholic neuropathy	G62.1
Alcoholic myopathy	G72.1
Alcoholic cardiomyopathy	I42.6
Alcoholic gastritis	K29.2
Alcoholic liver disease	K70
Alcoholic fatty liver	*K70.0*
Alcoholic hepatitis	*K70.1*
Alcoholic fibrosis and sclerosis of the liver	*K70.2*
Alcoholic cirrhosis of the liver	*K70.3*
Alcoholic hepatic failure	*K70.4*

Alcoholic liver disease, unspecified	*K70.9*
Alcohol-induced acute pancreatitis	K85.2
Alcohol-induced chronic pancreatitis	K86.0
Maternal care for (suspected) damage to fetus from alcohol	035.4
Fetus and newborn affected by maternal use of alcohol	P04.3
Fetal alcohol syndrome (dysmorphic)	Q86.0
Finding of alcohol in blood	R78.0
Toxic effect of alcohol	T51
Ethanol	*T51.0*
Methanol	*T51.1*
Other alcohols	*T51.8*
Alcohol unspecified	*T51.9*
Accidental poisoning by and exposure to alcohol	X45
Intentional self-poisoning by and exposure to alcohol	X65
Poisoning by and exposure to alcohol, undetermined	Y15
Evidence of alcohol involvement determined by blood alcohol level	Y90

Notes: According to Rehm et al. (2010).
ICD-10; International Classification of Diseses, 10th revision.
ICD codes in italic type represent subcodes within a main code of classification.

The detrimental consequences of alcohol consumption are reflected by the high proportions of patients being admitted to general hospitals due to alcohol-attributable diseases. Data from a study conducted in Germany revealed that 21.0% of the inpatients from one general hospital were treated for alcohol-attributable diseases (Gerke et al., 1997). Similar results are reported by a study from Spain, where 24.4% of the inpatients from a general hospital unit for internal medicine were admitted due to alcohol-attributable diseases (Jarque-Lopez et al., 2001). A study conducted in Scotland showed that 12.0% of general medical patients and 25.0% of gastroenterology patients were admitted due to alcohol-attributable diseases (Hislop and Heading, 2004). Furthermore, the prevalence of alcohol dependence and alcohol abuse in general hospitals is very high. For example, in one general hospital in Germany, the prevalence of alcohol dependence was reported to be 12.7%, and 4.8% of the inpatients were classified as alcohol abusers (Rumpf et al., 1998).

Previous studies on alcohol-attributable diseases and dose-response relations between volume of alcohol drinking and the risk of morbidity focussed on specific diseases and used data from one general hospital only or from special wards such as emergency rooms or gastroenterology

wards. Hitherto, there is no study on the association between volume of drinking and the risk of any alcohol-attributable disease analyzing data from more than one general hospital and more than one ward.

1.2 Motivation to change drinking behaviour and motivation to seek help for alcohol problem drinking

Given both the fact that general hospital inpatients are frequently found to have alcohol-attributable diseases and that the prevalence of alcohol dependence and abuse in general hospitals is very high, there is a need for appropriate treatment addressing the individual's alcohol problem. The general hospital seems to be a suitable setting for interventions. Being admitted to a hospital and being confronted with somatic consequences of alcohol drinking has been hypothesized to be a 'teachable moment' and a motivator to change problem drinking (Mitka, 1998). Hospitalization due to alcohol consumption provides also an opportunity to initiate first treatment with regard to alcohol problem drinking (Rumpf et al., 1999). An appropriate procedure is needed including screening for alcohol problems and intervention. For planning effective interventions, the inpatient’s motivational level has to be considered. A theoretical framework to explain motivation to change is given by the *Trans-Theoretical Model of Behaviour Change* (TTM; DiClemente and Prochaska, 1998). According to this model, motivation to change is conceptualized as a process differentiating the precontemplation, contemplation, preparation, action and maintenance stages. Individuals in the precontemplation stage are either ignorant of their drinking problem or unwilling to change their drinking behaviour. In the contemplation stage, individuals think seriously about change and evaluate the pros and cons both of the problem behaviour and the change. Individuals in the preparation stage intend to take action in the immediate future, while individuals in the action stage modify their behaviour or environment to overcome their problem. The maintenance stage is characterized by stabilizing behaviour change and avoiding relapse.

Motivation to seek help for alcohol problems can also be described using the stage model of behaviour change. Freyer et al. (2004) demonstrated that motivation to change and motivation to seek help were distinct, albeit positively correlated measurement constructs among high-risk drinkers. The authors also demonstrated that 42.0% of non-treatment seeking alcohol dependent individuals from general hospitals were characterized by different levels of motivation regarding motivation to change and motivation to seek help.

Based on the TTM, brief interventions as motivational interviewing have been developed. The TTM has been found to be a helpful concept for tailored interventions in medical settings. Providing brief interventions with respect to alcohol problems is necessary for two reasons: (1) alcohol problem drinking is expected to be practiced again after discharge, and (2) alcohol problem drinking may lead to a high number of re-admissions due to alcohol-attributable disorders. Thus, to initiate interventions addressing the inpatient's motivation to change drinking behaviour and motivation to seek help is an important public health priority.

One way to add to screening and early intervention according to problem drinking might be the use of routine treatment diagnoses classified by AAFs to detect inpatients with problem drinking and to initiate appropriate interventions in a time-saving manner. However, little is known about motivation to change and motivation to seek help in individuals with problem drinking and alcohol-attributable diseases. In particular, there is no study analyzing longitudinal data from general hospital inpatients with any alcohol-attributable disease.

1.3 Alcohol-attributable diseases and associated morbidity risk using the example of fatty liver disease and its association with blood pressure and hypertension

The general population of North-East Germany is characterized as a population at risk with a high prevalence of behavioural risk factors. With respect to alcohol consumption, it has been demonstrated that the prevalence of at-risk drinking was 14.1% in this population, and the prevalence of excessive drinking defined as the consumption of >5 drinks per day within the last 30 days was 43.1% (Baumeister et al., 2005). It is not surprising that alcohol-attributable diseases such as fatty liver disease (FLD) are also highly prevalent in this population: 37.6% of the male and 21.7% of the female population is affected (Völzke et al., 2007). Therefore, the region is particularly suitable to analyze FLD as an example for alcohol-attributable diseases in the general population.

FLD, the accumulation of fat in the liver exceeding 5.0% of liver weight, is a major cause of liver morbidity in Western countries (Fallo et al., 2008). In 2003, the estimated prevalence of FLD in Western countries in the general population ranged from 17.0% to 33.0% (Shifflet and Wu, 2009). FLD is mostly a benign condition, but may progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma in about 10% of patients (Gaemers and Groen, 2006).

The pathogenesis of FLD is complex and not fully elucidated yet, but seems to be multifactorial (Caballeria et al., 2007). Risk factors for developing FLD encompass components of the metabolic syndrome as well as alcohol consumption, nutritional disorders, surgical procedures and medication. However, Sanyal (2002) points out that fatty disorders of the liver have traditionally been defined as alcoholic and non-alcoholic but indicate that there is no consensus on the best way to classify FLD. Nevertheless, previous studies on FLD differentiated between alcoholic fatty liver disease and non-alcoholic fatty liver disease and commonly excluded individuals with high alcohol consumption (e.g. Bellentani et al., 2004; Tarantino et al., 2007). A systematic review on the multicausality of FLD by Völzke (submitted) adds to the debate on the distinction between alcoholic fatty liver disease and non-alcoholic fatty liver disease. Völzke (submitted) concludes that the distinction between alcoholic and "non-alcoholic" FLD should be replaced by a concept which regards FLD as a multicausal disorder.

Most patients with FLD are asymptomatic or may have unspecific symptoms as abdominal discomfort or fatigue. Therefore, physical examination does not reliably indicate the presence of FLD (Adams and Angulo, 2005; Neuschwander-Tetri, 2005). Liver biopsy is the gold standard for the diagnosis of FLD. However, this procedure is time-consuming and invasive with the risk of potential complications (Shifflet and Wu, 2009). In routine medical care, liver function tests including serum alanine aminotransferase (ALT) are used as screening tests to detect FLD. Although elevated ALT levels have been demonstrated to be the most reliable marker for FLD (Bellentani et al., 2000), liver enzymes may be within the reference range in up to 78.0% of patients and is thus insensitive for the detection of FLD (Adams and Angulo, 2005). Abdominal ultrasound is a more sensitive tool to detect FLD with a sensitivity varying from 60.0% to 94.0% and a specificity of 88.0% to 95.0% (Adams and Talwalkar, 2006). Thus, the combination of increased ALT levels and liver ultrasound to detect FLD might improve estimates of the prevalence of FLD.

As overweight and alcohol consumption are two main risk factors for FLD, prevention and treatment should focus on lifestyle modification including alcohol use, diet and exercise. Pharmacological interventions using drugs, which improve insulin resistance, can support treatment (Schreuder et al., 2008; Shifflet and Wu, 2009). However, risk factor reduction is the primary goal in prevention and treatment of FLD.

There is growing interest in research on the association between FLD and extrahepatic sequelae such as cardiovascular disease. In the context of the present dissertation, the association of FLD with blood pressure and hypertension was analyzed. Previously, numerous studies investigated the association between FLD and hypertension in different directions. For example, data from a clinical study of 30 patients with FLD showed that hypertension was present in 50.0% of the population (Cortez-Pinto et al., 1999). Likewise, the prevalence of hypertension was found to be 49.0% in a general population sample with FLD (Adams et al., 2009). Conversely, studies using data from hypertensive patients revealed prevalence rates of FLD of 30.9-55.8% (Donati et al., 2004; Fallo et al., 2009). Another study investigated the population-based prevalence of FLD and its risk factors and demonstrated that individuals with hypertension had a 1.4-fold higher chance for FLD compared to individuals without hypertension (Adams et al., 2009). However, the role of FLD in the development of hypertension has not been well investigated yet with only a few studies analyzing the longitudinal association of FLD with blood pressure-related variables and hypertension. As hypertension is more common in West Pomerania than in other regions of Germany (Meisinger et al., 2006), the chosen setting seems to be particularly suitable to analyze the association of FLD with blood pressure-related variables and hypertension.

1.4 Aims of the study

Based on the presented theoretical background, several research questions were derived. To answer these research questions, data from three studies were analyzed resulting in three scientific publications as basis for the present dissertation.

Aim 1: To provide data on alcohol-attributable diseases in general hospital inpatients with alcohol problem drinking. In detail, the main research question of study 1 was: Is there a dose-response relation between volume of drinking and the risk of diseases with different AAFs?

This question was answered in the first scientific paper:

> Lau, K., Freyer-Adam, J., Coder, B., Riedel, J., Rumpf, H.-J., John, U. and Hapke, U. (2008). Dose-response relation between volume of drinking and alcohol-related diseases in male general hospital inpatients. *Alcohol and Alcoholism, 43(1)*, 34-38.

Aim 2: To assess motivation to change drinking behaviour and motivation to seek help for alcohol problems at hospitalization as well as changes in motivation to change drinking

behaviour, motivation to seek help and in daily alcohol consumption across time in general hospital inpatients with alcohol problem drinking and alcohol-attributable diseases. In detail, the research questions of study 2 were: (a) Do general hospital inpatients having diseases with different AAFs differ with respect to motivation to change drinking behaviour and motivation to seek help for alcohol problems at hospitalization? (b) Do general hospital inpatients having diseases with different AAFs differ with respect to changes in motivation to change drinking behaviour, motivation to seek help and daily alcohol consumption within one year after hospitalization?

These questions were answered in the second scientific paper:

> Lau, K., Freyer-Adam, J., Gärtner, B., Rumpf, H.-J., John, U. and Hapke, U. (2010). Motivation to change risky drinking and motivation to seek help for alcohol risk drinking among general hospital inpatients with problem drinking and alcohol-related diseases. *General Hospital Psychiatry, 32(1)*, 86-93.

Aim 3: To investigate the association of FLD with blood pressure-related variables and hypertension in a general population sample. In detail, the research questions of study 3 were: Is there an association of FLD with blood pressure-related variables and hypertension at baseline and at 5-year-follow-up? Does alcohol consumption have an influence on the association of FLD with blood pressure-related variables and hypertension?

These questions were answered in the third scientific paper:

> Lau, K., Lorbeer, R., Haring, R, Schmidt, C.O., Wallaschofski, H., Nauck, M., John, U., Baumeister, S.E. and Völzke, H. (2010). The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study. *Journal of Hypertension, 8(9)*, 1829-1835.

2. METHODS

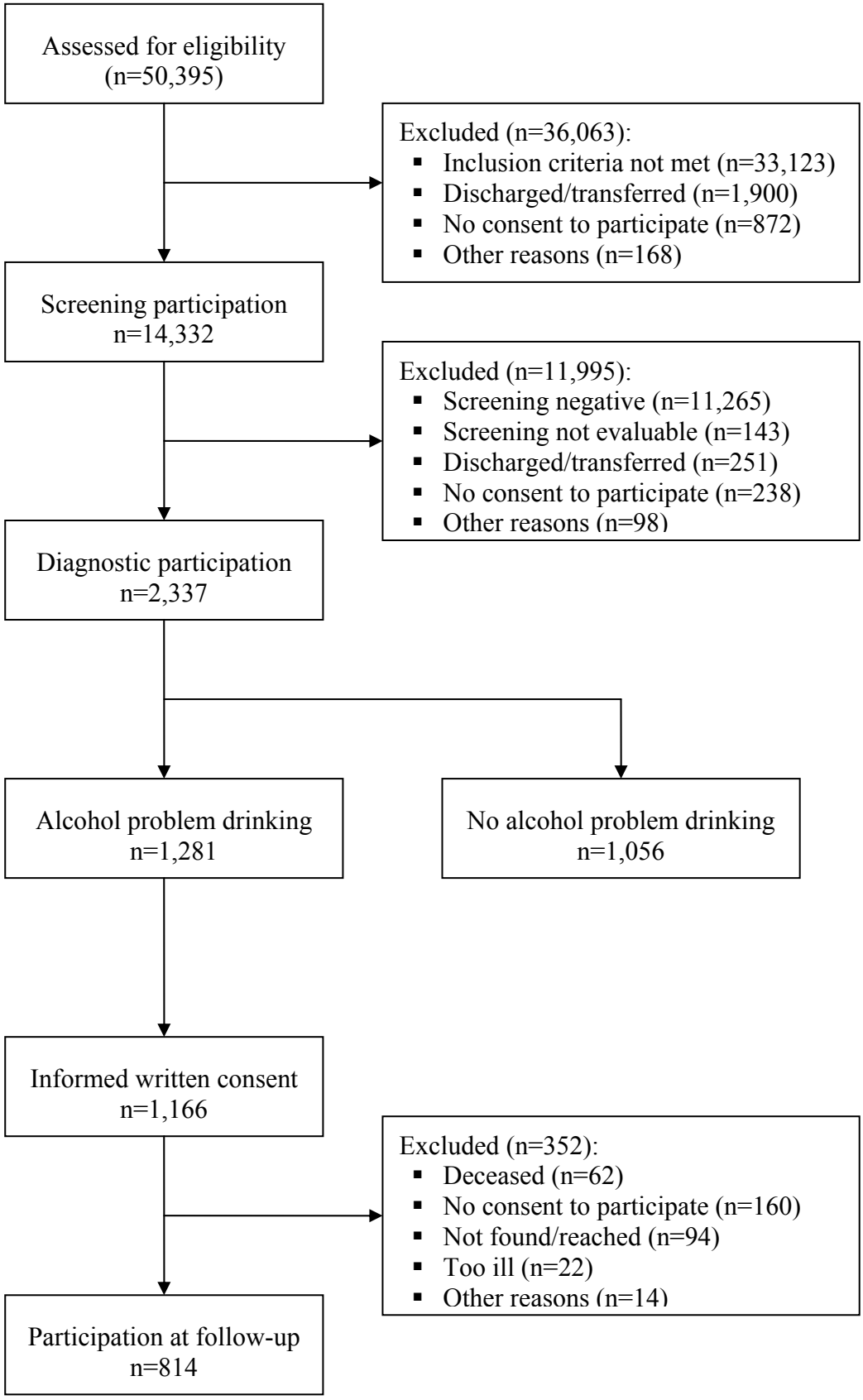
2.1 Study populations

Data for the present dissertation were derived from two studies: 'Early Intervention at General Hospitals' and 'Study of Health in Pomerania' (SHIP).

2.1.1 Early Intervention at General Hospitals

'Early Intervention at General Hospitals' is a randomized controlled trial designed to test the effectiveness of brief intervention among general hospital inpatients with alcohol problem drinking. Data for this study was collected between 28 April 2002 and 30 June 2004 at four general hospitals representing urban und rural areas in West Pomerania. These four hospitals encompassed a total of 29 wards. The sample recruitment procedure is depicted in Figure 1.
From 50,953 consecutive hospital admissions, 17,272 patients aged 18 to 64 years and staying at hospital for at least 24 hours were considered eligible for study participation and asked to consent to an alcohol screening. Patients physically and cognitively not capable to participate in the study, patients already recruited for the study during an earlier hospital stay, patients with language barriers and patients employed at the hospital were excluded. A total of 14,332 patients were screened for problem drinking, and a positive result was obtained for 2,924 patients. They were asked for further study participation, and those giving informed consent were then assessed for alcohol use disorders (n=2,337). In the diagnostic interview, 1,281 patients were found to be current alcohol problem drinkers (alcohol dependence, alcohol abuse, at-risk-drinking, heavy episodic drinking). Of these, 91.0% (n=1,166) gave informed consent for further participation in an intervention study. The patients received motivational interviewing based counselling either by a specialized liaison service, by hospital physicians or received hospital treatment as usual without additional counselling. Follow-up interviews were conducted on median 15 months after baseline, in which 814 patients (69.8% of eligible participants) took part. The study was approved by the Ethics Committee of the University of Greifswald.

Figure 1 **Flow chart of the sample recruitment in Early Intervention at General Hospitals**



Note: According to Freyer-Adam et al. (2008).

For the present dissertation, data from two different subsamples including patients with alcohol problem drinking and alcohol-attributable diseases were analyzed.

Study 1: Dose-response relation between volume of drinking and alcohol-related diseases

Of all patients with current problem drinking (n=1,281), 985 (76.9%) were identified as drinking above safe levels (>20/30 g per day). Ninety-one percent (n=899) gave informed consent for further study participation. The remaining inpatients refused study participation (n=54) or did not further take part in the study for other reasons, e.g. early discharge (n=32). Due to the low proportion of women in the sample (5.9%), all 53 women were excluded. Thus, the final sample consisted of 846 men.

Study 2: Motivation to change risky drinking and motivation to seek help for alcohol problem drinking

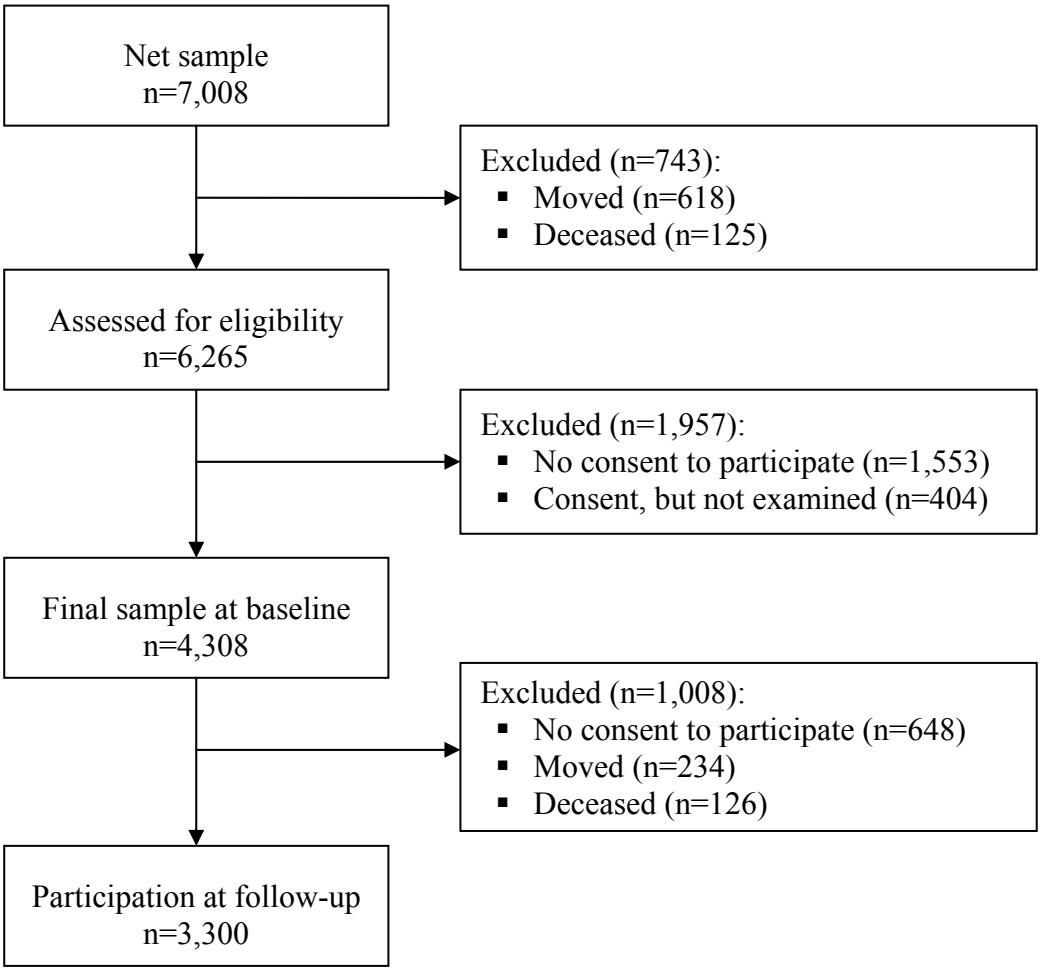
Of all patients with current problem drinking (n=1,281), 1,166 gave informed consent to participate in an intervention study. Patients received counselling either by a specialized liaison service, by hospital physicians or received hospital treatment as usual without additional counselling. In order to investigate the natural course of motivation to change drinking behaviour and of motivation to seek help, data from inpatients from the treatment as usual group were used (n=446). One year later, follow-up interviews were conducted in which 312 patients (70.0% of eligible participants) took part. Thus, the study population comprised of 312 patients. Hospital diagnoses were missing in 18 cases leading to a final study population comprising 294 inpatients with alcohol problem drinking and alcohol-attributable diseases.

2.1.2 Study of Health in Pomerania

SHIP is a population-based cohort study conducted in West Pomerania. The main objectives of SHIP are (a) to assess prevalence and incidence of common risk factors, subclinical disorders and clinical diseases, and (b) to investigate the complex associations among risk factors, subclinical disorders and clinical diseases. The study details are described in detail elsewhere (Völzke et al., 2010a).

The sample recruitment procedure is depicted in Figure 2. For the baseline examinations, a sample of 7,008 eligible individuals aged 20 to 79 years was drawn from population registries. Only individuals with German citizenship and main residency in the study area were included. The net sample (without migrated or deceased persons) comprised 6,265 eligible individuals. Selected persons received a maximum of three postal invitation letters. In case of non-response, letters were followed by a phone call or by home visits if contact by phone was not possible. The SHIP population finally included 4,308 participants (response 68.8%). Baseline examinations were conducted between 1997 and 2001. Between 2002 and 2006 all participants were re-invited for an examination follow-up, in which 3,300 individuals (83.5% of eligible persons) took part. Follow-up examinations were conducted on median five years after baseline. All participants gave informed written consent. The study protocol is consistent with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald. The study was monitored by a review board of independent scientists.

Figure 2 Flow chart of the sample recruitment in the Study of Health in Pomerania



For the present dissertation, data from the following subsample was analyzed:

Study 3: The association of fatty liver disease with blood pressure and hypertension

Of the 3,300 participants with follow-up data, 38 had an uncertain diagnosis of FLD, 12 were tested positive for hepatitis B surface antigen, 17 were tested positive for hepatitis C virus antibody, and 17 had a known history of liver cirrhosis. Furthermore, four participants lacked blood pressure measurement and 21 had missing ALT data. Overall, 109 participants were excluded leaving 3,191 individuals for the resulting analytical sample.

2.2 Measurements

In the following section, the main measurements conducted in 'Early Intervention at General Hospitals' and 'Study of Health in Pomerania' are described. A more detailed description of the measurement procedures is given in the respective papers.

2.2.1 Early Intervention at General Hospitals

Data on demographics including age, gender, having an intimate partner, having own children, employment status and school education as well as data on smoking status and cigarettes per day were obtained by a self-administered questionnaire.

All general hospitals provided one routine principal diagnosis and one secondary diagnosis based on ICD-10 coding for each inpatient. Disease conditions were classified according to their relation to alcohol consumption following the approach of Rehm et al. (2006a). ICD-10 codes indicating diseases 100% attributable to alcohol consumption by definition (e.g. alcoholic gastritis) were assigned an AAF of 1 (AAF=1). ICD-10 codes indicating diseases partially attributable to alcohol consumption (e.g. oesophageal cancer) were assigned an AAF of less than 1 (AAF<1). Diseases with no causal relation to alcohol consumption or diseases where alcohol consumption was found to have a preventive effect (e.g. type 2 diabetes mellitus) were assigned an AAF of 0 (AAF=0).

Alcohol consumption was assessed using the quantity-frequency questions of the German adaptation of the Composite International Diagnostic Interview (M-CIDI; Lachner et al., 1998; Wittchen and Pfister, 1997). Quantity was assessed using standard drinks. Standard drinks were converted into grams of pure alcohol, based on the type of the beverage and its volume percentage. Frequency was assessed using five categories: almost daily, 3-4 times a week, 1-2 times a week, 1-3 times a month, less than once a month. A quantity-frequency-index was computed using the mean of the frequency categories. The mean daily alcohol consumption was categorized into three groups: >120 g, 61-120 g and 31-60 g (Bühringer, 2002). Data on the number of drinking years were also derived from the M-CIDI.

Motivation to change drinking behaviour was assessed using the Readiness to Change Questionnaire (RCQ; Rollnick et al., 1992) which has been developed as a short measure of general stages of change. It consists of 12 items, four for each scale representing: Precontemplation (e.g. Drinking less alcohol would be pointless for me), Contemplation (e.g.

My drinking is a problem sometimes) and Action (e.g. I am trying to drink less than I used to).

The Treatment Readiness Tool (TReaT; Freyer et al., 2004) was administered to assess motivation to seek formal help for alcohol problems. It consists of 12 items, four for each readiness scale: Precontemplation (e.g. I do not think that other people can help me), Contemplation (e.g. I eventually may want help but not now), and Preparation (e.g. I have decided to seek appropriate treatment).

2.2.2 Study of Health in Pomerania

Baseline examinations in SHIP encompassed a broad spectrum of examinations including medical and dental examinations as well as a medical interview and a self-answering questionnaire. A detailed description of the examinations in SHIP is given elsewhere (Völzke et al., 2010a).

Data on demographics including age, gender and school education as well as data on behavioural risk factors (alcohol consumption, smoking, physical activity) and the individual's medical history and medication were obtained by a computer-assisted interview.

Somatometric examinations were conducted including body weight and height as well as waist circumference. Weight and height were measured for the calculation of the body mass index (BMI=weight [kg]/height² [m²]).

Sonographic examinations were performed by trained physicians using a 5 MHz transducer and a high resolution instrument (Vingmed VST Gateway Santa Clara, CA). The sonographers were unaware of the participant's clinical and laboratory characteristics.

For the laboratory examinations, non-fasting blood samples were drawn from the cubital vein in the supine position. Markers of hepatitis B virus (HBsAg) and hepatitis C virus infection (anti-HCV) were determined by enzyme-linked immunosorbent assays (AxSym HBSAG and AxSym HCV, Abbot, Abbot Park, USA). ALT levels were measured photometrically (Hitachi 704; Roche, Mannheim, Germany) and expressed as µmol/L x s, which corresponds to (µmol/L x s) x 60=IU/L.

FLD was defined as the presence of a hyperechogenic liver pattern, with evident density differences between hepatic and renal parenchyma together with increased serum ALT levels (>75th percentile) using four categories (Baumeister et al., 2008). Category 1 comprised individuals without hyperechogenic liver pattern and without increased serum ALT levels (US-/ALT-), category 2 individuals without hyperechogenic liver pattern and with increased serum ALT levels (US-/ALT+), category 3 individuals with hyperechogenic liver pattern and without increased serum ALT levels (US+/ALT-), and category 4 individuals with hyperechogenic liver pattern and with increased serum ALT levels (US+/ALT+).

Systolic and diastolic blood pressure were measured three times after a five minute rest period at the right arm of seated subjects using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan) with each reading being followed by a further rest period of three minutes. Blood pressure was measured between 8 am and 7 pm. One of two differently sized cuffs was applied according to the circumference of the participant's arm. The mean of the second and third measurement was calculated and used for the present analyses. Systolic and diastolic blood pressures of $\geq$140 mmHg and $\geq$90 mmHg, respectively, were considered increased. Hypertension was defined as increased systolic or diastolic blood pressure or use of antihypertensive medication.

Alcohol consumption was assessed using a beverage-specific quantity-frequency measure: number of days with alcohol consumption (beer, wine, spirits) and the quantity of alcohol consumed on such a day over the last month. Average daily consumption (in grams of pure ethanol) was calculated by multiplying frequency and amount of alcohol from beer, wine, and spirits, respectively, using a standard ethanol content of 4.8 percent (by volume) in beer, 11.0 percent (by volume) in wine, and 33.0 percent (by volume) in spirits (Bühringer, 2002). The average daily alcohol consumption was categorized with respect to at-risk drinking following the recommendations of the British Medical Association (BMA; 1995). The BMA regards an average daily alcohol consumption of more than 20 g for women and more than 30 g for men as at-risk drinking.

2.3 Statistical analyses

Data analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL), and Stata version 10.2 (StataCorp., College Station, TX).

2.3.1 Study 1: Dose-response relation between volume of drinking and alcohol-related diseases

Multinomial logistic regression analyses were performed to predict the risk of diseases with AAF=1 and AAF<1 by the daily alcohol consumption. Odds ratios (OR) and their 95% confidence interval (95% CI) are presented.

2.3.2 Study 2: Motivation to change risky drinking and motivation to seek help for alcohol problem drinking

Differences regarding motivation to change drinking behaviour and motivation to seek help at hospitalization between inpatients with diseases with AAF=0, inpatients with diseases with AAF<1 and inpatients with diseases with AAF=0 were analyzed using chi-square statistics. Three one-way-analyses of variance (ANOVA) with repeated measures were conducted to test for significant differences between the three AAF groups with respect to changes in motivation to change drinking behaviour, motivation to seek help and daily alcohol consumption across time. Svyset command in Stata was used to take into account clustering within wards. Clinical wards (n=29) were chosen as the primary sampling unit.

2.3.3 Study 3: The association of fatty liver disease with blood pressure and hypertension

Linear and logistic regression analyses were conducted to analyze (a) the association of FLD with blood pressure-related variables and hypertension at baseline, and (b) the association of baseline FLD with blood pressure-related variables and hypertension at follow-up. Adjusted means and their 95% CI or ORs and their 95% CI are presented. To test for the specific influence of alcohol consumption on the association of FLD with blood pressure-related variables and hypertension, interactions between FLD and alcohol consumption with respect to blood pressure-related variables and hypertension were calculated.

3. RESULTS

3.1 Study 1: Dose-response relation between volume of drinking and alcohol-related diseases (Lau, Freyer-Adam, Coder et al., 2008)

Among the study population, 26.6% of the inpatients had a disease with AAF=1 and 20.2% had a disease with AAF<1.

Multinomial regression analyses revealed that inpatients consuming >120 g and inpatients consuming 61-120 g of pure alcohol per day had a 6-fold and 3-fold higher chance for diseases with AAF=1, respectively, compared to inpatients consuming 31-60 g of pure alcohol per day (Table 2). Furthermore, inpatients consuming >120 g of pure alcohol per day had a 2-fold higher chance for diseases with AAF<1 compared to inpatients consuming 31-60 g of pure alcohol per day.

Table 2 Multinomial regression analysis (n=747)

	AAF=0	AAF=1		AAF<1	
		OR	CI (95 %)	OR	CI (95 %)
>120 g	Ref.	6.3	3.6-11.3	2.0	1.2-3.4
61-120 g	Ref.	2.9	1.6-5.1	1.0	0.6-1.5
31-60 g	Ref.	Ref.		Ref.	

Notes: Adjusted for age, intimate partner, children, employment status, school education, number of drinking years, smoking status and hospital.
OR, odds ratio.
CI, confidence interval.
Ref., reference group or category.
AAF=alcohol attributable fraction.

3.2 Study 2: Motivation to change risky drinking and motivation to seek help for alcohol problem drinking (Lau, Freyer-Adam, Gärtner et al., 2010)

3.2.1 Baseline differences in motivation based on groups of diseases with different alcohol-attributable fractions

Differences between the AAF groups regarding motivation to change drinking behaviour and motivation to seek help at baseline are shown in Table 3. The three groups differed significantly both in motivation to change drinking behaviour and in motivation to seek help. Regarding motivation to change drinking behaviour, the highest proportion of inpatients with AAF=1 was found to be in contemplation, while the highest proportion of inpatients with AAF<1 was found to be in action. Among inpatients with AAF=0, the highest proportion was found to be in precontemplation. Regarding motivation to seek help, the highest proportion of inpatients with AAF=1 was found to be in preparation, and the highest proportions of inpatients with AAF<1 and AAF=0 was found to be in precontemplation.

Table 3 Motivation to change drinking behaviour (RCQ) and motivation to seek help (TReaT) at baseline based on groups with different alcohol-attributable fractions of hospital diagnoses

	AAF=1	AAF<1	AAF=0	Design-based F (df)	p
RCQ (%)				6.71 (3.46, 96.99)	< .001
Precontemplation	11 (12.2)	10 (18.2)	60 (40.3)		
Contemplation	47 (52.2)	19 (34.6)	46 (30.9)		
Action	32 (35.6)	26 (47.3)	43 (28.9)		
TReaT (%)				16.17 (3.53, 98.93)	< .001
Precontemplation	20 (22.7)	26 (48.2)	89 (60.5)		
Contemplation	17 (19.3)	11 (20.4)	39 (26.5)		
Preparation	51 (58.0)	17 (31.5)	19 (13.0)		

Notes: using svyset commands (strata=hospital, primary sampling unit=clinical wards).
AAF=alcohol attributable fraction; RCQ=Readiness to Change Questionnaire (motivation to change drinking behaviour); TReaT=Treatment Readiness Tool (motivation to seek help).

3.2.2 Changes in motivation to change drinking behaviour, motivation to seek help and changes in daily alcohol consumption across time

The distribution of motivation to change drinking behaviour, motivation to seek help and daily alcohol consumption in the AAF groups at baseline and at follow-up is depicted in Table 4. Motivation to change drinking behaviour and motivation to seek help were used as continuous variables with larger means indicating higher motivation. Two repeated-measures ANOVAs were conducted to analyze differences in motivation to change drinking behaviour and in motivation to seek help across time in the three AAF groups. Corresponding to motivation to change drinking behaviour, changes in daily alcohol consumption were analyzed. Due to skewed data, the variable was log transformed for analysis.

Motivation to change drinking behaviour

Motivation to change drinking behaviour did not significantly change across time in any of the three AAF groups (F[1]=0.21, P=0.64). A main effect for group (F[2]=18.40, P<.001) was observed indicating that motivation to change drinking behaviour differed between the three AAF groups, with inpatients with AAF=1 and AAF<1 having a larger mean at both time points than inpatients with AAF=0. The group × time interaction was non-significant (F[2]=3.05, P= 0.05).

Motivation to seek help

Motivation to seek help significantly decreased in the three AAF groups across time (F[1]=21.03, P<.001). There was a significant main effect for group (F[2]=21.66, P<.001) indicating that motivation to seek help differed between the three AAF groups, with inpatients with AAF=1 having a larger mean across time than inpatients with AAF<1 and AAF=0. The group × time interaction was non-significant (F[2]=1.08, P= 0.34).

Daily alcohol consumption

The average daily alcohol consumption significantly decreased in the three AAF groups across time (F[1]=52.37, P<.001). There was a significant main effect for group (F[2]=2.87, P<.05) indicating that the average daily alcohol consumption differed between the three AAF groups, with inpatients with AAF=1 having a larger mean at both time points than inpatients with AAF<1 and AAF=0. A significant group × time interaction (F[2]=3.80, P<.05) was observed, indicating different time courses in the AAF groups.

Table 4 Motivation to change drinking behaviour, motivation to seek help and average daily alcohol consumption at baseline and at follow-up based on groups with different alcohol-attributable fractions of hospital diagnoses

		baseline		follow-up	
	N	M	SD	M	SD
Motivation to change drinking behaviour[a]					
AAF=1	74	2.20	0.66	2.34	0.80
AAF<1	51	2.33	0.74	2.33	0.86
AAF=0	140	1.88	0.82	1.64	0.78
Motivation to seek help[a]					
AAF=1	77	2.32	0.83	1.96	0.91
AAF<1	49	1.84	0.90	1.46	0.71
AAF=0	137	1.52	0.71	1.32	0.57
Daily alcohol consumption[b]					
AAF=1	80	149.95	121.80	61.83	94.72
AAF<1	53	115.66	121.81	44.98	69.04
AAF=0	141	75.83	94.08	48.51	58.93

Notes: Data are adjusted means; [a]adjusted for age, gram alcohol per day, smoking, having own children, employment status and hospital; [b]adjusted for age, smoking, having own children, employment status and hospital.
AAF=alcohol attributable fraction.

3.3 Study 3: The association of fatty liver disease with blood pressure and hypertension (Lau, Lorbeer, Haring et al., 2010)

Analyses in the whole study population revealed that individuals with liver hyperechogenity and with increased ALT levels showed higher odds for increased diastolic blood pressure and hypertension at baseline and for increased systolic blood pressure and hypertension at follow-up (Tables 5 and 6).

Table 5 Association of fatty liver disease with blood pressure-related variables and hypertension in the total sample at baseline (n=3,191)

	US- & ALT-	US- & ALT+	US + & ALT-	US + & ALT+
	N=1897	N=342	N=491	N=461
SBP; mmHg	144.7 (143.0-146.3)	146.0 (142.5-149.5)	144.8 (142.2-147.3)	146.7 (144.0-149.3)
DBP; mmHg	87.7 (86.7-88.6)	87.8 (85.8-89.8)	87.2 (85.7-88.7)	89.7 (88.1-91.2)
Systolic hypertension ≥140 mmHg	Ref.	0.9 (0.6-1.4)	0.8 (0.6-1.2)	1.1 (0.7-1.6)
Diastolic hypertension ≥90 mmHg	Ref.	1.1 (0.7-1.7)	0.9 (0.6-1.4)	1.6 (1.1-2.4) *
Hypertension	Ref.	1.2 (0.6-2.2)	0.9 (0.5-1.7)	2.8 (1.3-6.2) *

Notes: * $p<0.05$ compared with individuals without hyperechogenic liver pattern and without increased ALT levels; linear and logistic regression analyses. Data are given as adjusted mean (95% confidence interval) or odds ratio (95% confidence interval). ALT levels above the 75th percentile were considered increased.
Models were adjusted for age, sex, waist circumference, BMI, diabetes mellitus, mean daily alcohol consumption and the use of antihypertensive medication.
ALT=alanine aminotransferase; US=ultrasound; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Table 6 Association of baseline fatty liver disease with blood pressure-related variables and hypertension at follow-up in the total sample (n=3,191)

	US- & ALT-	US- & ALT+	US + & ALT-	US + & ALT+
	N=1897	N=342	N=491	N=461
SBP; mmHg	139.2 (137.5-141.0)	139.6 (136.0-143.2)	140.1 (137.4-142.7)	142.9 (140.2-145.7)
DBP; mmHg	83.8 (82.8-84.7)	82.7 (80.7-84.8)	83.3 (81.8-84.8)	86.2 (84.7-87.8)
Systolic hypertension ≥140 mmHg	Ref.	1.0 (0.6-1.5)	0.9 (0.6-1.3)	1.8 (1.2-2.6) *
Diastolic hypertension ≥90 mmHg	Ref.	0.9 (0.6-1.5)	0.7 (0.5-1.2)	1.3 (0.9-2.0)
Hypertension	Ref.	1.5 (0.9-2.5)	1.1 (0.7-1.8)	3.1 (1.7-5.8) *

Notes: * $p<0.05$ compared with individuals without hyperechogenic liver pattern and without increased ALT levels; linear and logistic regression analyses. Data are given as adjusted mean (95% confidence interval) or odds ratio (95% confidence interval). ALT levels above the 75th percentile were considered increased.
Models were adjusted for age, sex, waist circumference, BMI, diabetes mellitus, mean daily alcohol consumption and the use of antihypertensive medication.
ALT=alanine aminotransferase; US=ultrasound; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Additional analyses were performed after exclusion of all individuals receiving antihypertensive medication. Individuals with liver hyperechogenity and increased ALT levels showed a higher mean systolic and diastolic blood pressure and a higher odds ratio for increased systolic and diastolic blood pressure and hypertension compared to individuals without liver hyperechogenity and without increased ALT levels at both baseline and follow-up. Individuals without liver hyperechogenity and with increased ALT levels showed a higher odds ratio for hypertension compared to individuals of the reference group at baseline (Tables 7 and 8).

Table 7 Association of fatty liver disease with blood pressure-related variables and hypertension at baseline in the subgroup of individuals without antihypertensive medication (n=2,417)

	US- & ALT-	US- & ALT+	US + & ALT-	US + & ALT+
	N=1555	N=285	N=296	N=281
SBP; mmHg	129.7 (128.9-130.5)	131.3 (129.3-133.2)	131.6 (129.6-133.6)	133.8 (131.9-135.9) *
DBP; mmHg	81.6 (81.0-82.1)	82.4 (81.2-83.6)	82.5 (81.2- 83.7)	85.0 (83.7-86.2) *
Systolic hypertension ≥140 mmHg	Ref.	1.3 (0.8-1.7)	1.2 (0.9-1.6)	1.8 (1.3-2.4) *
Diastolic hypertension ≥90 mmHg	Ref.	1.5 (1.0-2.1)	1.1 (0.8-1.6)	1.7 (1.3-2.4) *
Hypertension	Ref.	1.5 (1.1-2.1) *	1.2 (0.9-1.7)	1.9 (1.3-2.6) *

Notes: * $p<0.05$ compared with individuals without hyperechogenic liver pattern and without increased ALT levels; linear and logistic regression analyses. Data are given as adjusted mean (95% confidence interval) or odds ratio (95% confidence interval). ALT levels above the 75th percentile were considered increased.
Models were adjusted for age, sex, waist circumference, BMI, diabetes mellitus and mean daily alcohol consumption.
ALT=alanine aminotransferase; US=ultrasound; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Table 8 Association of baseline fatty liver disease with blood pressure-related variables and hypertension at follow-up in the subgroup of individuals without antihypertensive medication (n=2,417)

	US- & ALT-	US- & ALT+	US + & ALT-	US + & ALT+
	N=1555	N=285	N=296	N=281
SBP; mmHg	128.1 (127.2-129.0)	128.7 (126.6-130.7)	127.7 (125.6-129.8)	131.6 (129.5-133.8) *
DBP; mmHg	80.7 (80.2-81.3)	80.7 (79.5-81.9)	80.5 (79.2-81.7)	83.4 (82.1-84.6) *
Systolic hypertension ≥140 mmHg	Ref.	1.2 (0.8-1.7)	1.1 (0.8-1.5)	1.7 (1.2-2.4) *
Diastolic hypertension ≥90 mmHg	Ref.	1.0 (0.7-1.5)	0.9 (0.6-1.4)	1.5 (1.1-2.1) *
Hypertension	Ref.	1.3 (0.9-1.8)	1.1 (0.8-1.6)	1.7 (1.2-2.3) *

Notes: * $p<0.05$ compared with individuals without hyperechogenic liver pattern and without increased ALT levels; linear and logistic regression analyses. Data are given as adjusted mean (95% confidence interval) or odds ratio (95% confidence interval). ALT levels above the 75th percentile were considered increased.
Models were adjusted for age, sex, waist circumference, BMI, diabetes mellitus and mean daily alcohol consumption.
ALT=alanine aminotransferase; US=ultrasound; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Interaction analyses were conducted to investigate whether alcohol consumption modifies the association of FLD with blood pressure-related variables and hypertension. The interactions between FLD and alcohol consumption with respect to all blood pressure-related variables and hypertension did not attain statistical significance (p=0.1-0.9). Therefore, analyses stratified by alcohol consumption were not performed.

4. DISCUSSION

4.1 Study 1: Dose-response relation between volume of drinking and alcohol-related diseases

4.1.1 Summary and interpretation in the context of current knowledge

In the present study, 46.8% of all inpatients with a daily consumption of more than 30 g of pure alcohol had a disease attributable to alcohol. Furthermore, data revealed a dose-response relation between the volume of alcohol consumed and the degree of AAF. Regarding diseases with AAF=1, inpatients consuming 61-120 g of pure alcohol per day had three times higher odds and inpatients consuming >120 g of pure alcohol per day had six times higher odds compared to inpatients consuming 31-60 g of pure alcohol per day. Moreover, inpatients consuming >120 g of pure alcohol per day were twice as likely to have a disease with AAF<1 than inpatients consuming 31-60 g of pure alcohol per day. The findings of the present study are in good agreement with results from other previous studies in Europe demonstrating a dose-response relation between volume of drinking and the risk of specific alcohol-attributable diseases (e.g. Anderson et al., 1993; Bondy et al., 1999; Corrao et al., 1999; Corrao et al., 2004). Moreover, the results of the present study support data from another German study which showed that 13.4% of all inpatients of a general hospital were treated for definitely alcohol-attributable diseases, and 39.1% were treated for possibly alcohol-attributable diseases (Gerke et al., 1997). However, this study was limited to one hospital and did not use international standards for the definition of alcohol-attributable diseases. The present study is the first one using AAFs to classify disease conditions according to their causal relationship with alcohol consumption and analyzing data from more than one general hospital of an entire region.

4.1.2 Strengths and limitations

Major strengths of the present study encompass the inclusion of data from four general hospitals representing urban and rural areas in West Pomerania and the consideration of any alcohol-attributable disease using AAFs to determine the degree of alcohol-relatedness of disease conditions. Nevertheless, a few limitations should be considered. First, the classification of disease conditions according to AAFs was based on the principal diagnosis and one secondary diagnosis only. As additional secondary diagnoses may have included diagnoses with AAF=1 or AAF<1, information on alcohol-attributable diseases might be

more reliable when considering more than one secondary diagnosis. However, not all hospitals supplied more than one secondary diagnosis. Second, the validity of the hospital diagnoses may be questionable as routine treatment diagnoses may have been biased by economic considerations of inpatient care. Third, women were excluded from the analyses. It might be argued that women are more vulnerable for somatic sequelae of alcohol consumption and that data on the proportions of diseases with different AAFs might thus be underestimated in the present study. Therefore, the present results can not be generalized to female general hospital inpatients with problem drinking in West Pomerania. Fourth, data on daily alcohol consumption were based on self-report only and may have been biased by under-reporting.

4.2 Study 2: Motivation to change risky drinking and motivation to seek help for alcohol problem drinking

4.2.1 Summary and interpretation in the context of current knowledge

Data from the present study revealed that the three AAF groups differed significantly regarding motivation to change drinking behaviour and motivation to seek help at hospitalization indicating that motivation and the degree of AAF are positively associated. Regarding motivation to change drinking behaviour, inpatients with AAF=1 and AAF<1 were more frequently found to be in contemplation and action, respectively, compared to inpatients with AAF=0. This finding strongly supports the hypothesis that hospitalization due to an alcohol-attributable disease serves as a motivator to change drinking behaviour stimulating processes of change such as consciousness-raising and self-reevaluation. Similar results are reported by Longabaugh et al. (1995) who investigated readiness to change in minor-injured patients with positive alcohol saliva tests at an emergency department. In this study, the more severe the injury had been the more likely was the patients' reports readiness to change.

Regarding motivation to seek help, inpatients with AAF=1 were most frequently found to be action compared to inpatients with AAF<1 and AAF=0. This finding might be explained by the fact that the group AAF=1 includes inpatients with alcohol dependence or severe psychiatric and somatic diseases caused by alcohol consumption. This result further indicates that hospitalization due to alcohol-attributable diseases is a 'teachable moment' that should be used for interventions addressing the inpatient's alcohol problem. For example, a referral to treatment as inpatient detoxification or self-help groups is appropriate for inpatients with alcohol dependence, while an intervention focussing on raising the awareness for alcohol problems should be considered for inpatients with at-risk drinking.

The idea of using the hospital stay as 'teachable moment' and as an opportunity to strengthen motivation to change drinking behaviour is further supported by the finding that the average daily alcohol consumption had decreased significantly within one year after hospitalization and that motivation to change drinking behaviour remained at same levels within one year in the three AAF groups. As motivation to seek help had decreased within one year after hospitalization, the hospital stay should be used to advance motivation to seek help for alcohol problems.

4.2.2 Strengths and limitations

Major strengths of the present study encompass the longitudinal design that allows for analyzing changes in motivation to change drinking behaviour, motivation to seek help and daily alcohol consumption across time. Furthermore, data from four general hospitals representing a variety of wards of one mixed rural and urban region were analyzed. A further strength of the present study is the consideration of any alcohol-attributable disease using AAFs to determine the degree of alcohol-relatedness of disease conditions. Nevertheless, a few limitations should be considered. First, the classification of disease conditions according to AAFs was based on the principal diagnosis and one secondary diagnosis only. As additional secondary diagnoses may have included diagnoses with AAF=1 or AAF<1, information on alcohol-attributable diseases might be more reliable when considering more than one secondary diagnosis. However, not all hospitals supplied more than one secondary diagnosis. Second, the validity of the hospital diagnoses may be questionable as routine treatment diagnoses may have been biased by economic considerations of inpatient care. Third, data on daily alcohol consumption were based on self-report only and may have been biased by under-reporting.

4.3 Study 3: The association of fatty liver disease with blood pressure and hypertension

4.3.1 Summary and interpretation in the context of current knowledge

In the present study, FLD as evidenced by liver hyperechogenity and increased ALT levels was associated with increased diastolic blood pressure and hypertension at baseline and with increased systolic blood pressure and hypertension at follow-up. In the subgroup of individuals not receiving antihypertensive drugs, FLD was associated with all blood pressure-

related variables and hypertension at baseline and follow-up. Furthermore, data revealed that this association was independent from alcohol consumption.

As the present results demonstrated most consistent associations between FLD und blood pressure-related variables and hypertension only in the subgroup of individuals not receiving antihypertensive drugs, it can be assumed that blood pressure lowering effects, which are highly variable across the different antihypertensive substances and dosages, may have biased the analyses in the whole study population.

The findings of the present study are in good agreement with other longitudinal studies demonstrating an association between FLD and hypertension. For example, Adams et al. (2009) found that individuals with FLD were more likely to develop hypertension compared to individuals without FLD over an 11-year-period. However, this study solely used elevated ALT levels to define FLD. As Palasciano et al. (2007) point out, blood tests cannot confirm the diagnosis of FLD, and liver imaging by ultrasound is a sensitive tool in the diagnosis of FLD. The findings of the present study are further in line with results from a clinical study using data of consecutive patients with FLD. In this study, 28.0% of the subjects developed hypertension in the period up to the follow-up examination. Nevertheless, FLD was inconsistently diagnosed using for example liver biopsy, ultrasound, computed tomography and laboratory findings (Friis-Liby et al., 2004). Similar results are reported from a case-control study analyzing the development of metabolic disorders in patients with FLD as defined by liver ultrasound (Fan et al., 2007). In this study, the incidence of hypertension at the end of follow-up was significantly higher in the FLD group compared to controls. The present study is the first population-based longitudinal study on the association between FLD, blood pressure and hypertension using liver ultrasound and blood testing to detect FLD.

Analyses further revealed that alcohol consumption did not contribute to the association of FLD with blood pressure-related variables and hypertension as interactions between FLD and alcohol consumption with respect to blood pressure-related variables and hypertension were non-significant. This finding indicates that the observed association of FLD with blood pressure-related variables and hypertension is not specific to alcohol consumption. This finding is in line with results from a Chinese population-based study (Zhou et al., 2007). Cross-sectional data analyses in that study likewise demonstrated that the association between FLD and blood pressure was independent of alcohol consumption. Also results from previous studies on the association between FLD and other outcomes such as serum insulin-like growth

factor-1 and serum testosterone levels in men using SHIP data were not modified by alcohol consumption (Völzke et al., 2010b; Völzke et al., 2009). Along with these findings, the results of the present study suggest that extrahepatic sequelae of FLD are at least partly independent of the factors that have caused FLD. The present findings further support the hypothesis that the etiology of FLD is multifactorial in which alcohol consumption is one risk factor among others, but not the determining risk factor.

4.3.2 Strengths and limitations

Major strengths of the present study encompass the population-based longitudinal design, the large sample size and the ultrasound examinations to detect FLD under strict quality management by standardized protocol and certified staff. Limitations may arise from the inability to perform liver biopsy in a large population-based study like SHIP due to ethical concerns, despite the fact that liver biopsy is the best diagnostic instrument to detect FLD.

4.4 Conclusion

The results of the present dissertation highlight the relevance of alcohol consumption for burden of disease and provide important implications for public health. In West Pomerania, alcohol-attributable diseases are frequently found in general hospital inpatients with problem drinking. The use of alcohol-attributable fractions to classify diseases according to their causal relationship with alcohol consumption might be a useful screening tool to detect problem drinkers. However, data on the proportions of alcohol-attributable diseases indicate that an approach to restrict screening for alcohol problem drinking to inpatients with alcohol-attributable diseases does not suffice as a considerable part of the inpatients had no alcohol-attributable disease and would be dismissed. A standard screening and diagnostic procedure in general hospitals to detect problem drinkers is needed. The present results further indicate that motivation to change drinking behaviour and motivation to seek help for alcohol problems and the degree of alcohol-relatedness of disease conditions are positively associated. Therefore, the use of alcohol-attributable fractions might also add to early intervention. Besides systematic screening for alcohol problem drinking, interventions corresponding to the inpatient's motivational level should be implemented in routine medical care. The findings regarding the association of fatty liver disease with blood pressure and hypertension suggest that alcohol-attributable diseases are also of high relevance in the general population and linked with further morbidity risk. Strengthening efforts in effective prevention measures to

reduce alcohol risk drinking and subsequent morbidity is therefore an important public health priority aim in the general population. Furthermore, the present findings suggest that the concept to distinguish between alcoholic and non-alcoholic origin of fatty liver disease might be obsolete and should be replaced by a concept that regards fatty liver disease as a multifactorial disease condition.

5. REFERENCES

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6. SCIENTIFIC PAPERS

The present dissertation is based on the following three scientific papers that are reprinted in this section. In addition, an overview of the first author's contribution to these publications is given.

1) Lau, K., Freyer-Adam, J., Coder, B., Riedel, J., Rumpf, H.-J., John, U. and Hapke, U. (2008). Dose-response relation between volume of drinking and alcohol-related diseases in male general hospital inpatients. *Alcohol and Alcoholism, 43(1)*, 34-38.

2) Lau, K., Freyer-Adam, J., Gärtner, B., Rumpf, H.-J., John, U. and Hapke, U. (2010). Motivation to change risky drinking and motivation to seek help for alcohol risk drinking among general hospital inpatients with problem drinking and alcohol-related diseases. *General Hospital Psychiatry, 32(1)*, 86-93.

3) Lau, K., Lorbeer, R., Haring, R, Schmidt, C.O., Wallaschofski, H., Nauck, M., John, U., Baumeister, S.E. and Völzke, H. (2010). The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study. *Journal of Hypertension, 8(9)*, 1829-1835.

Table 9 Overview of the first author's contribution to the scientific papers

Scientific paper	Conception and design	Data acquisition	Data analysis	Data inter-pretation	a) Writing draft b) Revision	Approval of final manuscript
(1) Lau, Feyer-Adam, Coder et al. (2008)	xx	n.a.	xxx	xxx	a) xxx b) xxx	yes
(2) Lau, Feyer-Adam, Gärtner et al. (2010)	xx	n.a.	xxx	xxx	a) xxx b) xxx	yes
(3) Lau, Lorbeer, Haring et al. (2010)	xx	n.a.	xxx	xxx	a) xxx b) xxx	yes

Notes: xxx=own responsibility, xx=conducted together with co-authors, x=collaboration, n.a.=not applicable.

6.1 Lau, K., Freyer-Adam, J., Coder, B., Riedel J., Rumpf, H.-J., John, U. and Hapke, U. (2008)

Dose-response relation between volume of drinking and alcohol-related diseases in male general hospital inpatients

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DOSE-RESPONSE RELATION BETWEEN VOLUME OF DRINKING AND ALCOHOL-RELATED DISEASES IN MALE GENERAL HOSPITAL INPATIENTS

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Abstract — Aims: Previous studies investigating dose-response relations between volume of drinking and diseases have focused on single diseases only. Until now, the relation between the drinking volume and the risk of having any alcohol-attributable disease is largely unknown. The aim of the present study is to investigate to what extent is the risk of diseases with different alcohol-attributable fractions (AAFs) predicted by daily alcohol consumption (>120 g, 61–120 g vs 31–60 g). **Methods:** The sample consisted of 805 inpatients classified as at-risk drinking, aged 18–64 years hailing from four general hospitals in North-eastern Germany. Inpatients were classified into three groups (AAF = 1, AAF < 1, AAF = 0). Group differences regarding alcohol-related variables, smoking, and demographics were analysed. A multinomial logistic regression analysis was conducted to predict the risk of diseases with AAF = 1 and AAF < 1. **Results:** In our sample, 26.6% of the inpatients showed a disease with AAF = 1, while 20.2% had a disease with AAF < 1. Inpatients consuming >120 g, and inpatients consuming 61–120 g revealed significantly higher odds for diseases with AAF = 1 compared to inpatients consuming 31–60 g (OR = 6.30, CI = 3.55–11.26; OR = 2.91, CI = 1.64–5.13). Regarding diseases with AAF < 1, inpatients consuming >120 g revealed significantly higher odds compared to the inpatients consuming 31–60 g (OR = 1.97, CI = 1.15–3.37). **Conclusions:** A dose-response relation between the level of the drinking volume and the risk of diseases with AAF = 1 was found in this sample of inpatients from the general hospitals.

INTRODUCTION

Alcohol consumption has been attributed to more than 60 medical conditions (Rehm *et al*., 2003a). Although many studies focus on alcohol-related mortality (Britton *et al*., 2003), little is known about alcohol-related diseases among the consumers who are still alive. In the past, research on alcohol-related health consequences has investigated dose-response relations between alcohol consumption and the risk of specific alcohol-related diseases. For example, a meta-analysis revealed a twofold increased risk of cirrhosis of the liver, a 24–31% increased risk of cancers of the pharynx and larynx, and a 40–70% increased risk of breast cancer for persons with a daily alcohol consumption of approximately 20 g compared to abstainers (Anderson *et al*., 1993). Another meta-analysis explored the association between alcohol consumption and the risk of 14 major alcohol-related neoplasms, non-neoplastic diseases, and injuries (Corrao *et al*., 2004). It revealed that the risk of cancer of the oral cavity, oesophagus and larynx, hypertension, liver cirrhosis, chronic pancreatitis, as well as injuries and violence, significantly increased with the amount of alcohol consumed starting from a daily consumption of 25 g compared to light consumption.

Alcohol consumption increases the craving for smoking in cigarette smokers and vice versa (Burton and Tiffany, 1997). Synergistic effects between alcohol consumption and tobacco smoking have been reported in several studies. For example, the two habits have a synergistic effect on the risk of oesophageal cancer among moderately exposed individuals (Castellsague *et al*., 1999).

Diseases may be classified according to their alcohol-attributable fractions (AAFs) into two groups (Rehm *et al*., 2006b): (i) Diseases wholly attributable to alcohol by definition (AAF = 1), e.g. alcoholic neuropathy and alcoholic gastritis, and (ii) diseases partially attributable to alcohol (AAF < 1), e.g. malignant neoplasms and cardiovascular diseases. AAFs have been defined as the proportion by which disease cases, injury events, or deaths would be reduced if alcohol use and misuse were eliminated among the population (Shultz *et al*., 1991).

Little is known about alcohol-attributable diseases among the general hospital inpatients. In general hospitals, inpatients with alcohol-related diseases seem to constitute a large proportion of the inpatients. In one hospital for example, 21% (29.3% of the men and 9.4% of the women) of the inpatients were found to have an alcohol-related disease (Gerke *et al*., 1997).

Previous studies on alcohol-related diseases contain several limitations: Firstly, only specific alcohol-related diseases were considered in the single studies (e.g. Anderson *et al*., 1993). Secondly, data was limited to one general hospital only (e.g. Gerke *et al*., 1997) or to one special ward, such as emergency rooms (e.g. McDonald *et al*., 2004). Thirdly, alcohol-related morbidity was not as well investigated as alcohol-related mortality (e.g. Britton and McPherson, 2001; Rehm *et al*., 2006a). Fourthly, the majority of studies on alcohol-related health consequences were based on older database using ICD-9 coding for medical conditions (e.g. Rehm *et al*., 2003b). Lastly, the volume of drinking was often categorized using non evidence-based threshold values (e.g. Boffetta *et al*., 2006).

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To our knowledge, there is no study providing data on alcohol-related diseases in the general hospitals from an entire geographical region encompassing the following conditions: (i) focusing on any alcohol-related diseases; (ii) comprising more than one general hospital and more than one ward; (iii) using ICD-10 coding for disease conditions; and (iv) categorizing alcohol consumption using evidence-based threshold values.

The aim of the present study is to provide data on alcohol-related diseases in a general hospital inpatient population with alcohol-related problems from one region of Germany and to investigate dose-response relations between the volume of drinking and alcohol-attributable diseases.

METHOD

Sample recruitment

Data for this study was collected as part of the intervention study 'Early Intervention in General Hospitals' (NCT 00423904, conducted by the Research Collaboration on Early Substance Use Intervention, EARLINT) between 28 April 2002 and 30 June 2004 at four general hospitals in Mecklenburg-Western Pomerania, Germany. These four hospitals provide medical care for the 198.745 inhabitants in the entire geographical region (Statistisches Landesamt, 2005). A total of 29 wards, including internal medicine, surgical medicine, dermatology, orthopedy as well as ear, nose, and throat units were included. The recruitment is described in more detail elsewhere (Freyer *et al*., 2007).

All inpatients between 18 and 64 years, with a minimum stay of 24 h were screened using the German Adaptation of the Alcohol Use Disorder Identification Test (AUDIT, Saunders *et al*., 1993) and the Luebeck Alcohol Screening Test (LAST, Rumpf *et al*., 1997) with cut-off values of eight and two, respectively. Patients meeting one or both of these cut-off values were considered to be screening positive. A positive screening result was obtained for 2337 inpatients and they were asked to further participate in the study. Those giving informed consent were then assessed using the alcohol section of the German adaptation of the computerized Composite International Diagnostic Interview (M-CIDI, Wittchen and Pfister, 1997; Lachner *et al*., 1998). The M-CIDI is a standardized software program based on DSM-IV (American Psychiatric Association, 1995) criteria. The alcohol section isolates current (past 12 months) from prior alcohol abuse and dependence. At-risk drinking was determined by a quantity-frequency-index based on the conventions of the BMA (British Medical Association, 1995). The BMA regards an average daily alcohol consumption of more than 20 g for women and more than 30 g for men as at-risk drinking. Another criterion for at-risk drinking was occasional heavy drinking, which was assessed with the question 'How often within the past 12 month did you drink five (for women) or eight (for men) drinks on one occasion?'. Inpatients reporting at least two times per month of drinking beyond the criterion mentioned were also considered as at-risk drinkers. Using the M-CIDI, 26.0% ($N = 608$) were classified as false-positives, 19.2% ($N = 448$) met the criteria for alcohol dependence in the past but not in the past 12 months and 54.8% ($N = 1281$) had a current alcohol problem (alcohol dependence, abuse, or at-risk drinking). Of these, 76.9% ($N = 985$) were identified as drinking beyond safe levels (>20/30 g). Ninety-one percent ($N = 899$) gave informed consent for further study participation. The remaining inpatients refused study participation ($N = 54$) or did not take further part in the study for other reasons, e.g. early discharge ($N = 32$). Because of the low proportion of women in the sample (5.9%), all 53 women were excluded. Thus, the final sample consisted of 846 men.

Hospital diagnoses

To classify inpatients into three groups of AAFs, all general hospitals provided one routine principal diagnosis and one secondary diagnosis for each inpatient. The diagnoses were based on ICD-10 (World Health Organization, 1992). Hospital diagnoses were missing for 41 inpatients which led to the exclusion of these cases from the final sample ($N = 805$). Classification of the hospital diagnoses was done according to their relation to alcohol following the approach of Rehm *et al*. (2006a). ICD-10 codes indicating diseases 100% attributable to alcohol by definition (e.g. alcoholic gastritis), were assigned an AAF of 1 (AAF = 1). ICD-10 codes indicating diseases partially attributable to alcohol (e.g. oesophageal cancer) were assigned an AAF of less than 1 (AAF < 1). Diseases with no causal relation to alcohol or diseases, where alcohol was found to have a preventive effect (e.g. diabetes mellitus) were assigned AAF = 0.

Measures

Alcohol consumption was assessed using the quantity-frequency questions of the M-CIDI. Quantity was assessed using the standard drinks. Standard drinks were converted into grams of pure alcohol, based on the type of the beverage and its volume percentage. Frequency was assessed using five categories: almost daily, 3–4 times a week, 1–2 times a week, 1–3 times a month, and less than once a month. A quantity-frequency-index was computed using the mean of the frequency categories. The mean alcohol consumption was categorized into three groups: >120, 61–120, and 31–60 g (Bühringer *et al*., 2002). The number of drinking years was calculated on the basis of the age of the onset of the highest lifetime alcohol consumption provided by the M-CIDI.

Smoking status was assessed on the basis of two conditions. First, inpatients were asked whether they had ever smoked about 100 or more cigarettes (yes/no). If so, they were asked 'Do you currently smoke?' with four response categories (yes, daily; yes, occasionally; no, for less than 6 months; no, for more than 6 months). Additionally, the mean number of cigarettes smoked per day was obtained.

The following demographics were assessed: age, having one intimate partner, having own children, employment status, and school education.

Data analysis

Descriptive statistics and a multinomial logistic regression analysis were conducted using SPSS 14.0 (SPSS Inc., Chicago, IL). For the effect size estimate we used Cramer's

Table 1. Description of the total sample ($N = 805$)

Variable	*N*	%
Age M (SD)	805	42.40 (11.13)
Has intimate partner	441	57.2
Has own children	547	68.5
Employment status		
Job-seeking	382	48.4
Full- or half-time	249	31.5
Others (e.g. retired, housewife)	159	20.1
School education		
<10 years	337	42.7
10–11 years	352	44.6
>11 years	101	12.7
Alcohol-attributable fraction (AAF)		
AAF = 1	214	26.6
AAF < 1	163	20.2
AAF = 0	428	53.2
Daily alcohol consumption		
>120 g	253	31.4
61–120 g	277	34.4
31–60 g	275	34.2
Smoking status		
Current daily	528	66.0
Current occasionally	46	5.8
Former	148	18.5
Never	78	9.7

Φ' for categorical variables and f for continuous variables (Cohen, 1988). Using ANOVAs and χ^2-statistics, group differences between inpatients with diseases with AAF = 1, with AAF < 1, and those with AAF = 0 regarding alcohol-related variables, smoking, and demographics were analysed. To identify group differences, Scheffé *post hoc* analyses were conducted for continuous variables. A multinomial logistic regression analysis was conducted to investigate the influence of drinking volume on the risk of diseases with AAF = 1, and on the risk of diseases with AAF < 1, with drinking category 31–60 g as reference category and AAF = 0 as the comparison group. Compared to logistic regression, multinomial logistic regression is more general because the dependent variable is not restricted to the two categories. We adjusted for group differences (age, intimate partner, children, employment status, school education, number of drinking years, and the smoking status) and for clustering at hospital levels. Odds ratios (OR) and 95% confidence intervals (CI) are reported.

RESULTS

Sample description

As depicted in Table 1, 26.6% of the inpatients had a disease with AAF = 1 and 20.2% had a disease with AAF < 1. Among the inpatients, 31.4% consumed >120 g, 34.4% consumed 61–120 g, and 34.2% consumed 31–60 g pure alcohol per day. The rate of the current smokers was 71.8%.

Characteristics of the AAF groups

The three AAF groups differed significantly in terms of alcohol-related variables, smoking, and demographics (Table 2). Compared to inpatients with diseases with AAF < 1 and AAF = 0, inpatients with diseases with AAF = 1 had the highest daily alcohol consumption, the highest proportion of inpatients who consumed >120 g per day and the highest proportion of current smokers. Compared to inpatients with AAF = 0, those with AAF = 1 smoked a higher number of cigarettes per day. Regarding cigarettes smoked per day, inpatients with diseases with AAF < 1 did not differ from those with AAF = 0. Inpatients with AAF < 1 were older and had a higher number of drinking years compared to inpatients with AAF = 1, but also compared to inpatients with AAF = 0. In our database, almost all medical conditions according to the classification of Rehm *et al*. (2006a) were found. Diseases not found in our database include certain forms of cancer (e.g. cancer of the lip), alcoholic cardiomyopathy, and ICD-10 codes starting with X, Y, or Z representing unintentional injuries. Regarding the single disease categories, the mean daily alcohol consumption ranged between 94.26 g (cerebrovascular diseases) and 127.39 g (diabetes mellitus).

Multinomial regression analysis

Inpatients consuming >120 g and inpatients consuming 61–120 g showed higher odds for diseases with AAF = 1 compared to inpatients consuming 31–60 g. Regarding diseases with AAF < 1, inpatients consuming >120 g showed increased odds compared to inpatients consuming 31–60 g (Table 3).

DISCUSSION

The three main findings of the study are: Firstly, 46.8% of all male inpatients admitted to the participating wards, and with a daily alcohol consumption of more than 30 g had a disease attributable to alcohol. Secondly, the data revealed a dose-response relation between the amount of alcohol consumed and the degree of AAF. Thirdly, an extremely high proportion of current smokers was found among the inpatients with alcohol-related problems.

Our findings support data from a different German study which showed that 13.4% of all inpatients of a general hospital were treated because of definitely alcohol-related diseases, and 39.1% were treated due to possibly alcohol-attributable diseases (Gerke *et al*., 1997). However, the study by Gerke *et al*. (1997) was limited to one hospital and this study suffered from not using international standards for the definition of alcohol-attributable diseases. Results from earlier studies demonstrating a dose-response relation between the volume of drinking and the risk of specific alcohol-related diseases (e.g. Anderson *et al*., 1993; Bondy *et al*., 1999; Corrao *et al*., 1999, 2004) were supported by our study. Our findings reveal that compared to inpatients consuming 31–60 g, the chances of having a disease with AAF = 1 was three times higher for inpatients consuming 61–120 g and six times higher for inpatients consuming >120 g. Moreover, inpatients consuming >120 g were twice as likely to have a disease with AAF < 1 than those inpatients consuming 31–60 g.

Table 2. Sociodemographic and alcohol-related characteristics of the sample based on groups with different alcohol-attributable fractions of hospital diagnoses

	AAF = 1		AAF < 1		AAF = 0				
Variables	*N*		*N*		*N*		F^a/χ^{2b} (df)	*P*	f^a/Φ'^b
Age M (SD)[c]	214	41.98 (8.20)	163	46.17 (9.41)	428	41.17 (12.62)	12.45 (2)	<0.001	0.18
Gram alcohol per day[d] M (SD)	214	173.37 (122.90)	163	123.63 (113.88)	428	95.48 (87.34)	40.50 (2)[f]	<0.001	0.31
Daily alcohol consumption (%)							102.39 (4)	<0.001	0.25
>120 g	120	56.1	51	31.3	82	19.2			
61–120 g	65	30.4	54	33.1	158	36.9			
31–60 g	29	13.5	58	35.6	188	43.9			
Drinking years[c] M (SD)	212	13.12 (10.25)	162	17.90 (11.59)	427	14.54 (11.29)	8.88 (2)	<0.001	0.14
Smoking status (%)							31.67 (6)	<0.001	0.14
Current daily	169	79.7	95	58.6	264	62.0			
Current occasionally	10	4.7	10	6.2	26	6.1			
Former	14	6.6	39	24.1	95	22.3			
Never	19	9.0	18	11.1	41	9.6			
Cigarettes per day[e] M (SD)	178	22.36 (9.95)	103	20.01 (10.21)	288	18.91 (9.19)	7.08 (2)	<0.01	0.14
Has intimate partner (%) yes	91	45.3	97	62.6	253	61.0	15.91 (2)	<0.001	0.14
Has own children (%) yes	138	65.7	128	78.5	281	66.1	9.48 (2)	<0.01	0.11
Employment status (%)							45.11 (4)	<0.001	0.17
Job-seeking	138	65.7	78	48.8	166	39.5			
Full- or half-time	42	20.0	41	25.6	166	39.5			
Others (e.g. retired, housewives)	30	14.3	41	25.6	88	21.0			
School education (%)							12.13 (4)	<0.05	0.09
<10 years	105	49.8	65	40.6	167	39.9			
10–11 years	92	43.6	70	43.8	190	45.3			
>11 years	14	6.6	25	15.6	62	14.8			

Notes: [a]continuous variables, [b]categorical variables, $\Phi' > 0.071$ small effect, $\Phi' > 0.212$ medium effect, $\Phi' > 0.354$ large effect, $f \geqslant 0.10$ small effect, $f \geqslant 0.25$ medium effect, $f \geqslant 0.40$ large effect. [c]Scheffé-Test show AAF = 1 < AAF < 1 > AAF = 0. [d]Scheffé-Test show AAF = 1 > AAF < 1 > AAF = 0. [e]Scheffé-Test show AAF = 1 > AAF = 0. [f]Due to skewed data, the variable was log transformed for analysis.

Table 3. Multinomial regression analysis ($N = 747$)

		AAF = 1		AAF < 1	
	AAF = 0	OR	CI (95%)	OR	CI (95%)
>120 g	Ref.	6.30	3.55–11.26	1.97	1.15–3.37
61–120 g	Ref.	2.91	1.64–5.13	0.95	0.59–1.51
31–60 g	Ref.		Ref.		Ref.

Notes: Adjusted for age, intimate partner, children, employment status, school education, number of drinking years, smoking status, and hospital. OR, odds ratio; CI, confidence interval; Ref., reference group or category.

The proportion of current smokers was extremely high in this sample of male inpatients with alcohol-related problems compared to the proportion of current smokers in the general population. This finding is in accordance with extremely high proportions of daily smokers found among persons who are at-risk drinking (John *et al*., 2003a), and also among alcohol dependent persons (Daeppen *et al*., 2000). Inpatients with AAF = 1 had a higher proportion of current smokers and were heavier smokers than the inpatients with AAF < 1, or AAF = 0. However, inpatients with AAF < 1 and those with AAF = 0 did not differ regarding smoking. Smoking may have added to diseases less than 100% attributable to alcohol, but also to those not attributable to alcohol (e.g. lung cancer). Several studies reported co-occurrence of diseases attributable to alcohol consumption and smoking (e.g. John *et al*., 2003b). Thus, it might be possible that the inpatients in our sample who are severely affected by diseases resulting from problematic drinking, could also be suffering from a tobacco-attributable disease, e.g. cancers of the trachea, bronchus and lung, or arteriosclerosis.

The present study adds new information on the following aspects: (i) A reduction in the sample selection bias by including four general hospitals representing a variety of wards of a mixed rural and urban region. (ii) Any alcohol-related diseases associated with inpatient hospital treatment in the study region were included. (iii) ICD-10 codes for disease conditions were used. (d) Alcohol consumption was assessed using evidence-based drinking categories.

A few limitations of the study should be considered. Firstly, our analyses are based on the principal diagnosis and on one secondary diagnosis only. As additional secondary diagnoses may have included diagnoses with AAF = 1 or AAF < 1, information on alcohol-related diseases might be more reliable when considering more than one secondary diagnosis. We were not able to consider several secondary diagnoses, because not all hospitals supplied more than one secondary diagnosis. Secondly, the validity of the hospital diagnoses may be questionable. We cannot rule out that diagnoses were biased because of economic considerations of inpatient care. Thirdly, according to Rehm's *et al*. (2006a) classification of diseases attributable to alcohol, the ICD-10 codes starting with X, Y, or Z representing unintentional

injuries did not appear in our database. Instead, unintentional injuries received codes starting with S and T, which were not classified by Rehm *et al*. (2006a). Thus, unintentional injuries were assigned AAF = 0, which may have led to an underestimation of diseases with AAF < 1. Fourthly, as we recruited inpatients with alcohol problems only, we did not have informed consent to obtain hospital diagnoses of inpatients with moderate alcohol consumption, or from the abstainers. Fifthly, women were excluded from our analyses.

We conclude that alcohol-related diseases are highly prevalent among male general hospital inpatients with alcohol-related problems, and that there is a dose-response relation between the volume of drinking and risk of diseases with AAF = 1.

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Motivation to change risky drinking and motivation to seek help for alcohol risk drinking among general hospital inpatients with problem drinking and alcohol-related diseases

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Motivation to change risky drinking and motivation to seek help for alcohol risk drinking among general hospital inpatients with problem drinking and alcohol-related diseases

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Abstract

Objective: The objective of this study was to analyze motivation to change drinking behavior and motivation to seek help in general hospital inpatients with problem drinking and alcohol-related diseases.
Method: The sample consisted of 294 general hospital inpatients aged 18–64 years. Inpatients with alcohol-attributable disease were classified according to its alcohol-attributable fraction (AAF; AAF=1, AAF<1 and AAF=0). Baseline differences in alcohol-related variables, demographics and motivation between the AAF groups were analyzed. Furthermore, differences in motivation to change, in motivation to seek help and in the amount of alcohol consumed from baseline to follow-up between the AAF groups were evaluated.
Results: During hospital stay, motivation to change was higher among inpatients with alcohol-attributable diseases than among inpatients who had no alcohol-attributable diseases [$F(2)=18.40$, $P<.001$]. Motivation to seek help was higher among inpatients with AAF=1 than among inpatients with AAF<1 and AAF=0 [$F(2)=21.66$, $P<.001$]. While motivation to change drinking behavior remained stable within 12 months of hospitalization, motivation to seek help decreased. The amount of alcohol consumed decreased in all three AAF groups.
Conclusions: Data suggest that hospital stay seems to be a "teachable moment." Screening for problem drinking and motivation differentiated by AAFs might be a tool for early intervention.

Keywords: Motivation; Alcohol-related diseases; Alcohol-attributable fractions; General hospital

1. Introduction

In general hospitals, inpatients with problem drinking are frequently found to have alcohol-related diseases. A study conducted in Germany showed that 21% of the inpatients of one general hospital were treated for alcohol-related diseases [1]. Data of a study conducted by Jarque-Lopez et al. [2] revealed that 24% of the inpatients of a general hospital unit for internal medicine in Spain were admitted due to alcohol-related disorders. In a study in Canada, 33.8% of malignant neoplasms and 57.9% of neuropsychiatric conditions in the male adult population were attributable to alcohol [3].

Due to the high proportion of general hospital inpatients with alcohol-attributable diseases, there is a need for appropriate treatment for three reasons. First, alcohol problem drinking may be expected to be practiced again after discharge. Second, alcohol problem drinking may lead to hospital readmission due to accompanying health problems. Third, being hospitalized due to alcohol-attributable disease may be a motivator to change problem drinking.

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Therefore, the hospital stay may be used for providing a brief intervention based on the inpatients' alcohol problem and motivational level.

From the point of view of hospital care and public health, it is important to find ways to screen for problem drinking in a time-saving manner. One opportunity to add to screening and early intervention according to alcohol problems might be to use routine treatment diagnoses classified by alcohol-attributable fractions (AAFs). Diseases may be classified according to their AAFs into two groups [4]: (a) diseases totally attributable to alcohol by definition (AAF=1; e.g., alcoholic neuropathy or alcoholic gastritis) and (b) diseases partially attributable to alcohol (AAF<1; e.g., esophageal cancer or hypertension). AAFs have been defined as the proportion by which disease cases, injury events or deaths would be reduced if alcohol use and misuse were eliminated among the population [5]. Specific AAFs have been found by analyzing survey data on per-capita alcohol consumption and relative risks for chronic diseases and injuries [6]. AAFs may be used for screening and counseling purposes.

Data on alcohol-related diseases provided so far by general hospitals have been largely limited to inpatients with alcohol dependence or alcohol abuse according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria [7]. However, the majority of general hospital inpatients with alcohol-attributable diseases are drinking an amount that is a risk for their health, but without fulfilling the criteria for alcohol dependence or abuse. Several definitions have been suggested for risky drinking. According to the definition of the British Medical Association (BMA) [8], an average daily alcohol consumption of more than 20 g for women and more than 30 g for men is regarded as risky drinking. Problem drinking may be defined as including risky drinking, as well as alcohol use disorders, according to *DSM-IV* criteria.

When screening for alcohol problem drinking and providing advice, inpatients' motivation to change drinking behavior and motivation to seek help for alcohol problems are important to consider. However, little is known about that among inpatients with problem drinking [9,10].

According to the Transtheoretical Model of Behavior Change (TTM), motivation to change drinking behavior may be conceptualized as a process differentiating the precontemplation, contemplation, action, preparation and maintenance stages [11]. Individuals in the precontemplation stage are either ignorant of their drinking problem or unwilling to change drinking. In the contemplation stage, individuals think seriously about change and evaluate the pros and cons both of the problem behavior and the change. Individuals in the preparation stage intend to take action in the immediate future, while individuals in the action stage modify their behavior or environment in order to overcome their problem. The maintenance stage is characterized by stabilizing behavior change and avoiding relapse.

From motivation to change, motivation to seek formal help for alcohol problems is distinguished. Motivation to seek help can also be described using the stage model of behavior change. Freyer et al. [12] demonstrated that motivation to change drinking behavior and motivation to seek help were distinct, albeit positively correlated, measurement constructs among high-risk drinkers. Although several criticisms of the TTM's theoretical aspects have been published, it has been proven particularly practicable in medical settings where its advantage of saving time is of particular note (cf., meta-analysis by Noar et al. [13]).

Previous studies on motivation and alcohol-related diseases contain several limitations. First, only specific diseases or injuries were considered as trauma [14]. Second, data were limited to alcohol-dependent individuals [15] or to special wards as emergency departments [16]. Third, the study design was cross-sectional and used small samples [9].

To our knowledge, there has been no study providing data on motivation and alcohol-related diseases that encompasses the following criteria: (a) focusing on any alcohol-related diseases; (b) providing data from general hospitals, including a variety of clinical wards; (c) including individuals with alcohol dependence, alcohol abuse and risky drinking; and (d) using longitudinal data. The aims of the present study were to investigate, first, whether having an alcohol-attributable disease may have an impact on the motivation to change problem drinking and on the motivation to seek help for alcohol problems and, second, whether the degree to which diseases are attributable to alcohol may have an impact on the motivation to change problem drinking and on the motivation to seek help for alcohol problems. To achieve these aims, we utilized data from general hospital inpatients with problem drinking and alcohol-related diseases.

2. Methods

2.1. Sample recruitment

Data for this study were collected as part of the study 'Early Intervention in General Hospitals' (NCT 00423904, Research Collaboration on Early Substance Use Intervention, EARLINT) between April 28, 2002 and June 30, 2004 at four general hospitals in Mecklenburg-Western Pomerania, Germany. These four hospitals provide medical care for 198,745 inhabitants in the comprised geographical region [17]. A total of 29 wards, including internal medicine, surgical medicine, dermatology and orthopedic wards, as well as ear, nose and throat units, were included. Recruitment is described in more detail elsewhere [18].

Among consecutively admitted inpatients aged between 18 and 64 years and with a minimum stay of 24 h, 14,322 were screened using the German adaptation of the Alcohol Use Disorders Identification Test (AUDIT) [19] and the Luebeck Alcohol Dependence and Abuse Screening Test [20], with 8 or more points and 2 or more points, respectively, indicating a positive screening result. This

was obtained for 2337 inpatients. They were asked for further study participation. Those giving informed consent were then assessed with respect to a diagnosis of alcohol use disorders according to *DSM-IV* [7] using the alcohol section of the German adaptation of the computerized Munich-Composite International Diagnostic Interview (M-CIDI) [21,22]. The alcohol section of the M-CIDI provides a lifetime diagnosis of alcohol abuse and dependence and whether the criteria for alcohol abuse or dependence have been fulfilled during the last 12 months prior to the interview. At-risk drinking was defined following the recommendations of the BMA [8] using data on inpatients' average daily alcohol consumption in the last 12 months prior to the interview. According to Babor and Grant [23], another criterion for risky drinking was heavy episodic drinking, which was assessed with the question 'How often within the past 12 months did you drink five (for women) or eight (for men) drinks on one occasion?' One standard drink corresponded to approximately 12 g of pure alcohol. Inpatients reporting at least two-times-per-month drinking above the criterion were also considered risky drinkers. With the use of the M-CIDI, 26.0% (n=608) were classified as false positives, 19.2% (n=448) met criteria for lifetime alcohol dependence but not in the past 12 months and 54.8% (n=1281) were considered current alcohol problem drinkers (alcohol dependence, alcohol abuse or risky drinking). Of these, 91.0% (n=1166) gave informed consent for further participation in an intervention study. The patients received motivational-interviewing-based counseling [24] either by a specialized liaison service or by hospital physicians, or received hospital treatment as usual without additional counseling. As we aimed to investigate the natural course of motivation to change and the natural course of motivation to seek help, we only used inpatients from the treatment-as-usual group (n=446). One year later, follow-up interviews in which 312 subjects (70.0% of eligible participants) took part were conducted. Of the 312 individuals with follow-up data, 18 lacked hospital diagnoses. These cases were excluded from our analyses, leaving 294 individuals for the resulting analytical sample.

2.2. Hospital diagnoses

To classify inpatients into three groups of AAFs, we used one routine principal diagnosis and one routine secondary diagnosis of the hospital for each inpatient. The diagnoses were based on *International Classification of Diseases, Tenth Revision* (*ICD-10*) [25]. Classification of the hospital diagnoses was performed according to their relation to alcohol following the approach of Rehm et al. [6]. *ICD-10* codes indicating diseases that are 100% attributable to alcohol by definition were assigned an AAF of 1 (AAF=1). *ICD-10* codes indicating diseases that are partially attributable to alcohol were assigned an AAF of less than 1 (AAF<1). Diseases with no relation to alcohol or diseases where alcohol was found to have potentially a preventive effect (e.g., diabetes mellitus) [26] were assigned an AAF of 0.

2.3. Measures

The Readiness to Change Questionnaire (RCQ) [27] was used to assess motivation to change. It was developed as a short measure of the general stages of change. It consists of 12 items, four for each scale, representing precontemplation (e.g., "Drinking less alcohol would be pointless for me"), contemplation (e.g., "My drinking is a problem sometimes") and action (e.g., "I am trying to drink less than I used to"). The 5-point Likert scale ranges from *strongly disagree* (−2) to *strongly agree* (2). The quick method allocates individuals to three stages (precontemplation, contemplation and action) based on the highest scale scores. In the case of between-scale ties, individuals are allocated to the higher motivational stage. Heather et al. [28] reported a good validity of the RCQ in predicting behavior change over time.

The Treatment Readiness Tool (TReaT) [12] was administered to assess motivation to seek formal help for alcohol problems. It is a short reliable measure based on the stages of change of the TTM [29,30]. It has 12 items, four for each readiness scale: precontemplation (e.g., "I do not think that other people can help me"), contemplation (e.g., "I eventually may want help but not now") and preparation (e.g., "I have decided to seek appropriate treatment"). The instruction refers to formal help for alcohol-related problems (including both professional treatment and self-help groups) on a dichotomous item response scale (true/not true). In conformity with the quick method of the RCQ [27], subjects are allocated to stages based on their highest scale score. In case of between-scale ties, subjects are allocated to the one further along on the motivational process. In the case of zero scores on all three scales, participants are assigned to precontemplation [31]. In contrast to persons in precontemplation or contemplation stage, persons in preparation stage intend to utilize formal help.

Alcohol consumption was assessed using the quantity–frequency questions of the M-CIDI. We did not use standard drinks to assess the quantity of alcohol consumption. Instead, an open question assessed the quantity of alcohol consumed on a typical drinking day, which was converted (beverage specific) into index units (one unit corresponded to 9 g of pure alcohol). Frequency was assessed using five categories: *almost daily*, *three to four times a week*, *one to two times a week*, *one to three times a month* and *less than once a month*. A quantity–frequency index was computed using the mean of the frequency categories. Outliers regarding daily alcohol consumption were determined using the mean plus three standard deviations (mean+3 S.D.). Cases above the threshold values of 500.41 g at baseline (seven outliers) and 346.54 g on follow-up (four outliers) were assigned these scores as maximum consumption. Due to skewed data, the variable was log transformed for analyses. The following demographics were assessed: age, having an intimate partner, having own children, employment status and school education.

2.4. Data analysis

Descriptive statistics and three one-way analyses of variance (ANOVA) with repeated measures adjusted for differences between the AAF groups at baseline were conducted using STATA Version 10 (StataCorp., College Station, TX). As the complex sampling strategy in this study required adjustments in calculating standard errors, all analyses were calculated using svyset commands, with hospital (n=4) as strata and ward (n=29) as primary sampling unit. Svyset in STATA allows considering sample survey data with cluster sampling, as used in this study. With the use of ANOVA and chi-square statistics, group differences in alcohol-related variables, demographics, motivation to change and motivation to seek help between inpatients with diseases with AAF=1, inpatients with diseases with AAF<1 and inpatients with diseases with AAF=0 were analyzed. To identify group differences, we conducted Scheffé post hoc analyses for continuous variables. Two repeated-measures ANOVA adjusted for age, gram of alcohol per day, smoking, having own children, employment status and hospital were used to verify significant differences in motivation to change and motivation to seek help across time. To analyze differences in average daily alcohol consumption across time, another repeated-measures ANOVA, adjusted for age, smoking, having own children, employment status and hospital, was conducted. Individuals with missing values were deleted listwise.

3. Results

3.1. Description of the total sample

Ninety-one percent (n=268) of the inpatients were male, and the mean age was 40.59 years (S.D.=11.97). Thirty-one percent of the inpatients suffered from a disease with AAF=1, and 19% had a disease with AAF<1. Among the sample, 50% were alcohol dependents, 12% were alcohol abusers and 38% were risky drinkers.

The frequent diseases of inpatients according to *ICD-10* [25] are displayed in Table 1. Regarding the principal diagnosis and the secondary diagnosis, the most common disease groups were injury and poisoning, mental and behavioral disorders, and diseases of the circulatory system.

3.2. Characteristics of the AAF groups at baseline

Table 2 depicts the characteristics of the AAF groups regarding alcohol-related variables and demographics at baseline. Significant differences were found for all variables, except school education and having an intimate partner. Inpatients with AAF=1 reported a higher average alcohol consumption than those with AAF=0. Compared to inpatients with AAF<1 and AAF=0, those with AAF=1 included the highest proportion of jobseekers and current smokers. Inpatients with AAF<1 were older, and more of them had children than inpatients in the other groups.

Table 1
Occurrence of diseases of inpatients according to *ICD-10*

Disease categories	Principal diagnosis		Secondary diagnosis	
	n	%	*n*	%
Certain infectious and parasitic diseases	3	1.2	1	0.4
Neoplasms	15	5.8	9	5.6
Endocrine, nutritional and metabolic diseases	2	0.8	16	6.3
Mental and behavioral disorders	60	23.3	63	24.9
Diseases of the nervous system	6	2.3	8	3.2
Diseases of the circulatory system	28	10.9	33	13.0
Diseases of the respiratory system	14	5.4	13	5.1
Diseases of the digestive system	21	8.1	38	15.0
Diseases of the skin	8	3.1	5	2.0
Diseases of the musculoskeletal system	16	6.2	6	2.4
Injury, poisoning	65	25.2	41	16.2
Others	20	7.7	20	5.9

3.3. Motivation to change and motivation to seek help at baseline

Baseline differences in motivation to change and motivation to seek help between the AAF groups are shown in Table 3. The three groups differed significantly in motivation to change and in motivation to seek help. Regarding motivation to change, the highest proportion of inpatients with AAF=1 were found to be in contemplation stage, while the highest proportion of inpatients with AAF<1 were found to be in action stage. Among inpatients with AAF=0, the highest proportion was found to be in precontemplation stage. Regarding motivation to seek help, the highest proportion of inpatients with AAF=1 were found to be in preparation stage, and the highest proportion of inpatients with AAF<1 and AAF=0 were found to be in precontemplation stage.

3.4. Motivation to change and motivation to seek help across time

The distribution of motivation to change and motivation to seek help in the AAF groups at baseline and on follow-up is displayed in Table 4. Motivation to change and motivation to seek help were used as continuous variables, with larger means indicating higher motivation. Two repeated-measures ANOVA were conducted to analyze differences in motivation to change and in motivation to seek help across time between the three groups. Corresponding to motivation to change drinking behavior, we analyzed changes in daily alcohol consumption.

3.4.1. Motivation to change

Motivation to change did not significantly change across time in any of the three AAF groups [$F(1)=0.21$, $P=.64$]. We observed a main effect for group [$F(2)=18.40$, $P<.001$] indicating that motivation to change differed between the three AAF groups, with inpatients with AAF=1 and AAF<1 having a larger mean at both time points than inpatients with AAF=0. The Group×Time interaction was nonsignificant [$F(2)=3.05$, $P=.05$].

Table 2
Characteristics of the sample at baseline based on groups with different AAFs of hospital diagnoses[a]

Variables	*n*	AAF=1	*n*	AAF<1	*n*	AAF=0	Design-based *F* (*df*)	*P*
Age [mean (S.D.)][b]	90	42.63 (7.35)	55	45.22 (11.23)	149	37.64 (13.63)	8.50 (2, 27)	<.01
Grams of alcohol per day [mean (S.D.)][c]	84	152.99 (125.81)	54	114.02 (121.25)	147	81.05 (103.75)	12.64 (2, 27)[d]	<.001
Smoking status (%)								
Current	77	86.5	33	61.1	108	72.5	4.02 (3.28, 81.90)	<.01
Former	5	5.6	14	29.9	29	19.5		
Never	7	7.9	7	13.0	12	8.1		
Has intimate partner (% yes)	47	56.0	34	64.2	83	58.9	0.48 (1.71, 42.69)	NS
Has own children (% yes)	61	68.5	42	76.4	84	56.8	3.83 (1.87, 46.82)	<.05
Employment status (%)								
Job-seeking	51	58.6	27	49.1	55	37.4	3.05 (3.18, 79.58)	<.05
Full time or part time	17	19.5	15	27.3	60	40.8		
Others (e.g., retired, housewives)	19	21.8	13	23.6	32	21.8		
School education (%)								
<10 years	37	42.1	20	37.7	54	36.5	0.93 (3.60, 90.11)	NS
10–11 years	45	51.1	24	45.3	70	47.3		
>11 years	6	6.8	9	17.0	24	16.2		

NS, not significant.
[a] Using svyset commands (strata=hospital; primary sampling unit=clinical wards).
[b] Scheffé test shows AAF=1, AAF<1>AAF=0.
[c] Scheffé test shows AAF=1>AAF=0.
[d] Due to skewed data, the variable was log transformed for analysis.

3.4.2. Motivation to seek help

Motivation to seek help significantly decreased in the three AAF groups across time [$F(1)=21.03$, $P<.001$]. There was a significant main effect for group [$F(2)=21.66$, $P<.001$] indicating that motivation to seek help differed between the three AAF groups, with inpatients with AAF=1 having a larger mean at both time points than inpatients with AAF<1 and AAF=0. The Group×Time interaction was nonsignificant [$F(2)=1.08$, $P=.34$].

3.4.3. Daily alcohol consumption

The average daily alcohol consumption significantly decreased in the three AAF groups across time [$F(1)=52.37$, $P<.001$]. There was a significant main effect for group [$F(2)=2.87$, $P<.05$] indicating that the average daily alcohol consumption differed in the three AAF groups, with inpatients with AAF=1 having a larger mean at both time points than inpatients with AAF<1 and AAF=0. A significant Group×Time interaction [$F(2)=3.80$, $P<.05$] indicating different time courses in the AAF groups was observed.

4. Discussion

The main findings of our study are as follows. First, the three AAF groups differed significantly in motivation to change and in motivation to seek help while hospitalized, indicating that motivation and the degree to which diseases are attributable to alcohol are positively associated. Second, motivation to change remained at the same levels after 12 months in the three AAF groups, while motivation to seek help decreased. Third, inpatients in all three AAF groups decreased their alcohol consumption within 12 months after hospitalization.

The high proportion of inpatients in precontemplation stage in terms of motivation to change and motivation to seek help among those with AAF=0 on hospitalization might be explained by the fact that these inpatients do not suffer from health consequences due to their alcohol consumption. As they have not yet suffered from alcohol-related health consequences, they are possibly not aware of their problem drinking or they neglect it. Therefore, they are neither

Table 3
Motivation to change (RCQ) and motivation to seek formal help (TReaT) at baseline based on groups with different AAFs of hospital diagnoses[a]

	AAF=1	AAF<1	AAF=0	Design-based *F* (*df*)	*P*
RCQ (column %)					
Precontemplation	11 (12.2)	10 (18.2)	60 (40.3)	6.71 (3.46, 96.99)	<.001
Contemplation	47 (52.2)	19 (34.6)	46 (30.9)		
Action	32 (35.6)	26 (47.3)	43 (28.9)		
TReaT (column %)					
Precontemplation	20 (22.7)	26 (48.2)	89 (60.5)	16.17 (3.53, 98.93)	<.001
Contemplation	17 (19.3)	11 (20.4)	39 (26.5)		
Preparation	51 (58.0)	17 (31.5)	19 (13.0)		

[a] Using svyset commands (strata=hospital; primary sampling unit=clinical wards).

Table 4
Motivation to change, motivation to seek help and average daily alcohol consumption at baseline and on follow-up in the AAF groups

	n	Baseline		Follow-up	
		Mean	S.D.	Mean	S.D.
Motivation to change[a]					
AAF=1	74	2.20	0.66	2.34	0.80
AAF<1	51	2.33	0.74	2.33	0.86
AAF=0	140	1.88	0.82	1.64	0.78
Motivation to seek help[a]					
AAF=1	77	2.32	0.83	1.96	0.91
AAF<1	49	1.84	0.90	1.46	0.71
AAF=0	137	1.52	0.71	1.32	0.57
Daily alcohol consumption[b]					
AAF=1	80	149.95	121.80	61.83	94.72
AAF<1	53	115.66	121.81	44.98	69.04
AAF=0	141	75.83	94.08	48.51	58.93

Data are adjusted means.
[a] Adjusted for age, gram of alcohol per day, smoking, having own children, employment status and hospital.
[b] Adjusted for age, smoking, having own children, employment status and hospital.

motivated to change their drinking behavior nor motivated to seek help.

The highest proportion of inpatients with AAF<1 were found to be in the action stage to change drinking behavior on hospitalization. This finding suggests that these inpatients might be aware of their disease being associated with their alcohol consumption. Even for inpatients with AAF<1, the experience of being admitted to a hospital seems to support motivation to change drinking behavior. Being confronted with a somatic sequela from drinking is a factor that may stimulate processes of change, such as consciousness raising and self-reevaluation [32]. Similar results have been reported by Longabaugh et al. [10], who investigated readiness to change in minor-injury patients at an emergency department. In this study, the more severe had been the injury, the more likely was the patient to report readiness to change. Regarding motivation to seek help while being hospitalized, the highest proportion of inpatients with AAF=1 was found to be in preparation stage. One plausible explanation for this finding is that the group AAF=1 includes inpatients with alcohol dependence or severe psychiatric and somatic disorders caused by alcohol (e.g., alcoholic polyneuropathy and alcoholic gastritis). The high proportion of individuals in preparation to seek help among those with AAF=1 indicates that hospitalization due to alcohol-related diseases is a "teachable moment" that should be used for interventions.

Our data further show that motivation to change remained stable in the three AAF groups within 12 months after hospitalization, while motivation to seek help for alcohol problems decreased. Similar results have been reported by Freyer et al. [31], who investigated motivation to change and motivation to seek help in a sample of alcohol-dependent individuals. They found that 42% of the individuals were characterized by different levels of motivation to change and motivation to seek help. The authors argue that a high self-efficacy might explain the combination of high motivation to change and low motivation to seek help. Another possible explanation for the present finding might be that inpatients who were highly motivated to change their drinking behavior on hospitalization and who managed to reduce their consumption or to become abstinent no longer considered that external help is still necessary for them. Thus, this finding supports the idea of using hospital stay as an opportunity to strengthen motivation to change and to advance motivation to seek help for alcohol problems.

The average daily alcohol consumption had decreased significantly 12 months after hospitalization in the three AAF groups. This result suggests that hospital stay might support a decrease in the amount of drinking. Also, having been interviewed extensively about drinking behavior might have stimulated contemplation about drinking and might have supported a decrease in drinking. Furthermore, underreporting of drinking amounts may have played a role in all patients who took part in follow-up inquiry.

The data on the proportions of alcohol-attributable diseases among this sample of problem drinkers indicate that an approach to restrict the screening for alcohol problem drinking to inpatients with alcohol-attributable diseases does not suffice. A considerable part of the inpatients has no alcohol-attributable diagnosis and would be dismissed. A standard screening and diagnostic procedure in general hospitals is needed to find problem drinkers among the inpatients.

We analyzed the patients in three AAF groups, assuming equal distances between the single AAF groups with increasing degree of alcohol involvement. To analyze the inpatients' motivation to change and to seek help, an obvious strategy would be a two-step procedure: First, to compare all inpatients with any alcohol-attributable disease versus all inpatients without any alcohol-attributable disease and, second, to analyze the subgroup of inpatients with alcohol-attributable disease along the AAF.

The strength of this study is that four general hospitals that provide inpatient medical treatment for an entire area of residence have participated in the diagnostic process that has been used. The limitations of the study are as follows. First, it has been conducted in a high-per-capita-consumption country; hence, proportions of patients with risky drinking or alcohol use disorders and alcohol-attributable disease may be expected to be particularly high compared to countries with a lower per-capita consumption. Second, our final sample is restricted to a treatment-as-usual group in an intervention study that, in addition, provided information in a 12-month follow-up. This may have increased sample selection bias towards better-off individuals in terms of disease and problem drinking. Third, the proportion of women was only 9% in the present study. This may be explained by the use of a non-gender-specific recommended AUDIT cutoff value of 8 [33], which might have caused an

underrepresentation of women with less severe alcohol problems. We decided not to drop the women from the analyses, as the study was designed to identify inpatients with an AUDIT score of 8 or higher. However, our analyses are not generalizable to women with problem drinking. Fourth, routine treatment diagnoses may have been biased by the treating physician and/or diagnostic-related groups as the leading diagnostic system is the leading principal for the reimbursement of treatment costs. Fifth, the proportion of alcohol-attributable diagnoses may have been confounded by the quality of addiction treatment services. The study region was largely rural in its nature and localized in Eastern Germany, where the addiction treatment system with outpatient counseling facilities and self-help groups is not as well developed as in other areas in Germany. Sixth, sociodemographic factors such as a high rate of unemployment may have biased the high proportions of inpatients with alcohol-attributable diseases and motivation to change drinking behavior.

In conclusion, as both motivation to change and motivation to seek help and the degree to which the inpatients' diseases were attributable to alcohol were positively associated on hospitalization, hospital stay should be used for interventions. Also, the hospital stay itself seems to have an intervention effect, showing a reduction in drinking amount in all three AAF groups. The use of AAFs might be an approach to detect inpatients with problem drinking and to provide interventions addressing the inpatients' alcohol problem. As inpatients' alcohol problems include alcohol dependence, abuse and risky drinking, there is a need for special interventions considering also the inpatients' motivational level. These interventions are aimed at different targets (e.g., raising awareness on alcohol problems in individuals with risky drinking and referral to treatment for inpatient detoxification to achieve abstinence in individuals with alcohol dependence). However, a brief intervention differentiated by the three groups of problem drinkers is not yet sufficiently comprehensive for use in general hospital care.

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The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study

The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study

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Objective **The aim of the present study was to investigate the association of fatty liver disease (FLD) with blood pressure (BP) and hypertension in a general population sample with prospective 5-year follow-up examinations.**

Design and methods **We used data from the Study of Health in Pomerania, conducted in the northeastern part of Germany. The study population comprised 3191 individuals aged 20–79 years. FLD was defined as the presence of a hyperechogenic pattern of the liver and increased serum alanine transferase (ALT) levels.**

Results **Multivariable analyses revealed that FLD was associated with increased DBP and hypertension at baseline and with increased SBP and hypertension at follow-up. In individuals with FLD, the chance of hypertension at baseline and follow-up was three-fold higher [odds ratio (OR) 2.8; 95% confidence interval (CI) 1.3–6.2 and OR 3.1; 95% CI 1.7–5.8, respectively] compared to individuals without FLD. In the subgroup of individuals not receiving antihypertensive medication, FLD was associated with all BP-related variables at baseline and follow-up. Analyses further suggest that these associations were independent of alcohol consumption and further confounders.**

Conclusion **FLD defined by liver hyperechogenity and increased ALT levels is associated with progression of BP over time and incident hypertension. In individuals with FLD, BP should be checked regularly and interventions addressing behavioural risk factors for FLD and hypertension should be initiated if necessary. Ultrasound should be implemented as a method to detect FLD in individuals with increased ALT levels in routine medical care.** ***J Hypertens*** **28:000–000 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: blood pressure, fatty liver disease, hypertension, longitudinal study

Abbreviations: ALT, serum alanine transferase; anti-HCV, marker of hepatitis C virus infection; DBP, diastolic blood pressure; FLD, fatty liver disease; HBsAg, marker of hepatitis B virus; SBP, systolic blood pressure; SHIP, Study of Health in Pomerania

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Introduction

Fatty liver disease (FLD) is becoming a major public health problem in Western countries [1,2]. Evidence suggests that components of the metabolic syndrome including obesity, diabetes, hypertriglyceridaemia and hypertension are major correlates of FLD, but the relative role of each of these factors in FLD is still undefined [3].

Numerous studies have investigated the association between FLD and hypertension. Data from a clinical study of 30 patients with FLD showed that hypertension was present in 50% of the population [4]. Likewise, the prevalence of hypertension was found to be 49% in a general population sample with FLD [5]. Conversely, studies using data from hypertensive patients revealed prevalence rates of FLD of 30–56% [6,7]. Another study investigated the population-based prevalence of FLD and its risk factors and demonstrated that individuals with hypertension had a 1.4-fold higher risk for FLD compared to individuals without hypertension [8]. However, the role of FLD as risk factor for hypertension has not been well investigated yet using prospective data with only a few studies analysing the longitudinal association between FLD and blood pressure (BP) [5,9,10].

In routine medical care, liver function tests including serum alanine aminotransferase (ALT) are used as screening tests to detect FLD. As Palasciano and colleagues [11] pointed out, laboratory-based tests cannot confirm the diagnosis of FLD. A more sensitive tool to detect FLD is abdominal ultrasound. Thus, the combination of increased ALT and liver ultrasound to detect FLD might improve estimates of the prevalence of FLD and will allow to assess the hypothesized risk of subsequent hypertension more precisely.

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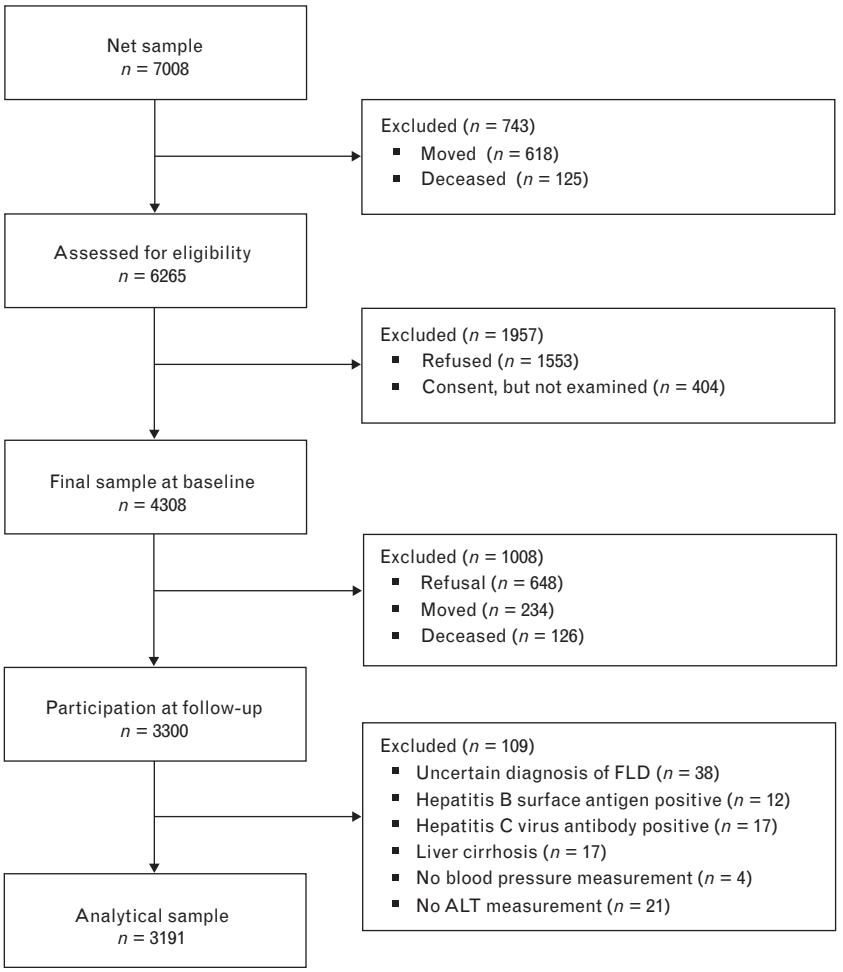
Fig. 1



Flow-chart according to sample recruitment.

Many causative factors are associated with FLD including components of the metabolic syndrome as well as alcohol consumption, nutritional disorders, surgical procedures and medication [8,12]. Nevertheless, previous studies on the association between FLD and hypertension differentiated between nonalcoholic fatty liver disease and alcoholic fatty liver disease and commonly excluded individuals with high alcohol consumption [6,8,13]. However, as the pathogenesis of FLD seems to be multifactorial [14]; we hypothesized that FLD *per se* determines the risk of hypertension and that there is no difference in the association between FLD and blood pressure (BP) when considering alcohol consumption.

To our knowledge, there is no previous research providing data on the association between FLD and BP encompassing the following criteria within one study: using a general population sample with a large sample size; using both liver ultrasound and blood testing to detect FLD; and using longitudinal data.

The aims of the present study were, first, to investigate the association of FLD with BP and hypertension, and, second, to determine whether there is a specific contribution of alcohol consumption to this association. To achieve these aims, we used data from a general population sample of adults from West Pomerania, the northeastern part of Germany. In this population, hypertension is more common than in other German regions [15]. Therefore, the chosen setting seems to be particularly suitable for the present analysis.

Methods

Setting and study population

The Study of Health in Pomerania (SHIP) is a population-based longitudinal study conducted in West Pomerania, the northeast area of Germany. The sample recruitment procedure is displayed in Fig. 1. For the baseline examinations, a sample of 7008 eligible participants aged 20–79 years was drawn from population registries. Only individuals with German citizenship

and main residency in the study area were included. The net sample (without migrated or deceased persons) comprised 6265 eligible participants. Selected persons received a maximum of three postal invitation letters. In case of nonresponse, letters were followed by a phone call or by home visits if contact by phone was not possible. The SHIP population finally included 4308 participants (response 68.8%). Baseline examinations were conducted between 1997 and 2001. Between 2002 and 2006 all participants were re-invited for an examination follow-up, in which 3300 participants (83.5% of eligible persons) took part [16]. Follow-up examinations were conducted on average 5.3 years after baseline. All participants gave informed written consent. The study protocol is consistent with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald. The study was monitored by a review board of independent scientists.

Of the 3300 participants with follow-up data, 38 had an uncertain diagnosis of fatty liver, 12 were tested positive for hepatitis B surface antigen, 17 were tested positive for hepatitis C virus antibody, and 17 had a known history of liver cirrhosis. Furthermore, four participants lacked BP measurement and 21 had missing ALT data. Overall, 109 participants were excluded from our analyses, leaving 3191 individuals for the resulting analytical sample.

Measurements

Baseline data included ultrasound of the liver, laboratory, and somatometric examinations as well as data on demographics, behavioural risk factors and the individual's medical history and medication. Sonographic examinations were performed by trained physicians using a 5 MHz transducer and a high-resolution instrument (Vingmed VST Gateway, Santa Clara, California, USA). The sonographers were unaware of the participant's clinical and laboratory characteristics. In SHIP, ultrasound examinations and readings underlie strict quality standards [17].

For the laboratory examinations, nonfasting blood samples were drawn from the cubital vein in the supine position. The laboratory takes part quarterly in the official national German external proficiency testing programmes. In addition, internal quality controls were analysed daily. Markers of hepatitis B virus (HBsAg) and hepatitis C virus infection (anti-HCV) were determined by enzyme-linked immunosorbent assays (AxSym HBSAG and AxSym HCV; Abbot, Abbot Park, Illinois, USA). ALT levels were measured photometrically (Hitachi 704; Roche, Mannheim, Germany) and expressed as μmol/l $\times$ s, which corresponds to (μmol/l $\times$ s) $\times 60 =$ IU/l.

FLD was defined as the presence of a hyperechogenic liver pattern, with evident density differences between hepatic and renal parenchyma [3,18,19] together with increased serum ALT levels (>75th percentile) using four categories [20]. Category 1 comprised individuals without hyperechogenic liver pattern and without increased serum ALT levels (US−/ALT−), category 2 individuals without hyperechogenic liver pattern and with increased serum ALT levels (US−/ALT+), category 3 individuals with hyperechogenic liver pattern and without increased serum ALT levels (US+/ALT−), and category 4 individuals with hyperechogenic liver pattern and with increased serum ALT levels (US+/ALT+).

SBP and DBP were measured three times after a 5-min rest period at the right arm of seated participants using a digital BP monitor (HEM-705CP; Omron Corporation, Tokyo, Japan) with each reading being followed by a further rest period of 3 min. BP was measured between 0800 and 1900 h. One of two differently sized cuffs was applied according to the circumference of the participant's arm. The mean of the second and third measurement was calculated and used for the present analyses. SBP and DBP of at least 140 and 90 mmHg, respectively, were considered increased. Hypertension was defined as increased SBP or DBP or use of antihypertensive medication.

The somatometric measures included body weight and height as well as waist circumference. Height and weight were measured for the calculation of the body mass index [BMI = weight (kg)/height^2 (m^2)]. Waist circumference was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the participant standing comfortably with weight distributed evenly on both feet.

Data on demographics, behavioural risk factors including physical activity, alcohol consumption, and smoking status were collected using computer-aided personal interviews. The following demographic variables were assessed: sex, age and school education. Individuals who participated in physical training during summer or winter for at least 1 h a week were classified as being physically active. Alcohol consumption was assessed using a beverage-specific quantity-frequency measure: number of days with alcohol consumption (beer, wine, spirits) and the quantity of alcohol consumed on such a day over the last month. Average daily consumption (in grams of pure ethanol) was calculated by multiplying frequency and amount, using beverage-specific standard ethanol contents. According to smoking habits, participants were categorized into current, former, and never smokers. Data on diabetes mellitus and antihypertensive medication were obtained by the individual's medical history.

Statistical analyses

Categorical data are given as numbers or percentages; continuous data are given as means and standard deviations. The study population was divided into four groups according to the presence or absence of a hyperechogenic liver pattern and increased serum ALT levels at baseline.

Table 1 Baseline characteristics of the study sample with and without sonographic fatty liver disease and increased alanine aminotransferase levels

	US− and ALT− ($N=1897$)	US− and ALT+ ($N=342$)	US+ and ALT− ($N=491$)	US+ and ALT+ ($N=461$)
BMI (kg/m^2), M (SD)	25.8 (4.3)	27.2 (3.8)**	29.6 (4.6)**	30.7 (4.3)**
Waist circumference (cm), M (SD)	83.5 (12.3)	91.2 (10.7)**	95.9 (11.6)**	101.9 (10.9)**
Sex (% male)	676 (35.6)	260 (76.0)**	238 (48.5)**	358 (77.7)**
Age (years), M (SD)	47.5 (15.7)	42.1 (13.8)**	59.8 (11.9)**	51.9 (12.4)**
School education (%)		*	**	**
<10 years	578 (30.5)	78 (22.8)	282 (57.6)	199 (43.2)
10 years	969 (51.1)	197 (57.6)	152 (31.0)	207 (44.9)
>10 years	350 (18.5)	67 (19.6)	56 (11.4)	55 (11.9)
Physical activity (% active)	897 (47.3)	166 (48.5)	164 (33.4)**	170 (36.9)**
Alcohol consumption (g/day), M (SD)	11.0 (17.0)	18.9 (39.5)**	13.5 (24.7)	21.5 (26.3)**
Smoking (%)		**	*	**
Never-smoker	754 (39.8)	95 (27.8)	203 (41.3)	133 (28.9)
Ex-smoker	603 (31.8)	119 (34.8)	180 (36.7)	209 (45.3)
Current smoker	539 (28.4)	128 (37.4)	108 (22.0)	119 (25.8)
Diabetes mellitus (%)	66 (3.5)	12 (3.5)	87 (17.8)**	64 (14.0)**

Pearson χ^2 and ANOVAs were used for bivariate comparisons with US− and ALT− as the reference group. Data are given as mean (SD) or number (%). ALT, alanine aminotransferase; ANOVA, analysis of variance; US, ultrasound. $^*P<0.01$. $^{**}P<0.001$.

Using ANOVAs and χ^2-statistics, differences between the FLD groups regarding demographics, somatometric variables, behavioural risk factors and diabetes mellitus at baseline were analysed. To identify group differences, Scheffé post-hoc analyses were conducted for continuous variables. Multivariable statistical analyses on the association between FLD and BP-related variables were performed using linear and logistic regression analyses. We adjusted for age, sex, waist circumference, BMI, diabetes mellitus, average daily alcohol consumption and the use of antihypertensive medication. We further performed interaction analyses to test for the specific influence of alcohol consumption on the association between FLD and BP-related variables. Adjusted means or odds ratios (OR) and their 95% confidence intervals (CI) were calculated. To evaluate possible bias due to missing data of individuals who did not participate at follow-up examinations, we repeated all analyses using weighted data. A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with STATA version 10 (StataCorp, College Station, Texas, USA).

Results

At baseline, there were 952 (29.8%) individuals with hyperechogenic ultrasound pattern of the liver, and 803 (25.2%) had increased serum ALT levels. Characteristics of the individuals in the four FLD groups are presented in Table 1. Significant differences were found for all considered variables. Individuals without liver hyperechogenity and without increased serum ALT levels were the reference group. Individuals with hyperechogenic pattern of the liver and with increased ALT levels showed a higher BMI, a higher waist circumference, were more often male and reported a higher average daily alcohol consumption compared to individuals of the reference group. Individuals with hyperechogenic pattern of the liver and without increased ALT levels were older, reported more often less than 10 years of schooling and were less physically active compared to individuals of the reference group. Moreover, they reported less often current smoking and more often former or never smoking compared to individuals of the reference group. They also reported more often diabetes mellitus. Individuals without hyperechogenic pattern of the liver and with increased ALT levels reported more often at least 10 years of schooling compared to individuals of the reference group.

Table 2 shows results of cross-sectional associations from multivariable models of the four FLD groups with BP-related variables in the total sample at baseline. Compared to individuals without liver hyperechogenity and without increased ALT levels, those with liver

Table 2 Association between fatty liver disease and blood pressure-related variables in the total sample at baseline ($n=3191$)

	US− and ALT− ($N=1897$)	US− and ALT+ ($N=342$)	US+ and ALT− ($N=491$)	US+ and ALT+ ($N=461$)
SBP, mmHg	144.7 (143.0–146.3)	146.0 (142.5–149.5)	144.8 (142.2–147.3)	146.7 (144.0–149.3)
DBP, mmHg	87.7 (86.7–88.6)	87.8 (85.8–89.8)	87.2 (85.7–88.7)	89.7 (88.1–91.2)
Increased SBP (≥140 mmHg)	Ref.	0.9 (0.6–1.4)	0.8 (0.6–1.2)	1.1 (0.7–1.6)
Increased DBP (≥90 mmHg)	Ref.	1.1 (0.7–1.7)	0.9 (0.6–1.4)	1.6 (1.1–2.4)*
Hypertension	Ref.	1.2 (0.6–2.2)	0.9 (0.5–1.7)	2.8 (1.3–6.2)*

Data are given as adjusted mean (95% CI) or odds ratio (95% CI). ALT levels above the 75th percentile were considered increased. Models were adjusted for age, sex, waist circumference, BMI, diabetes mellitus, mean daily alcohol consumption and the use of antihypertensive medication. $^*P<0.05$ compared with participants without hyperechogenic liver pattern and without increased ALT levels; linear and logistic regression analyses. ALT, alanine aminotransferase; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; US, ultrasound.

Table 3 Association between baseline fatty liver disease and blood pressure-related variables at follow-up in the total sample ($n = 3191$)

	US− and ALT− ($N = 1897$)	US− and ALT+ ($N = 342$)	US+ and ALT− ($N = 491$)	US+ and ALT+ ($N = 461$)
SBP, mmHg	139.2 (137.5–141.0)	139.6 (136.0–143.2)	140.1 (137.4–142.7)	142.9 (140.2–145.7)
DBP, mmHg	83.8 (82.8–84.7)	82.7 (80.7–84.8)	83.3 (81.8–84.8)	86.2 (84.7–87.8)
Increased SBP (≥140 mmHg)	Ref.	1.0 (0.6–1.5)	0.9 (0.6–1.3)	1.8 (1.2–2.6)*
Increased DBP (≥90 mmHg)	Ref.	0.9 (0.6–1.5)	0.7 (0.5–1.2)	1.3 (0.9–2.0)
Hypertension	Ref.	1.5 (0.9–2.5)	1.1 (0.7–1.8)	3.1 (1.7–5.8)*

Data are given as adjusted mean (95% CI) or odds ratio (95% CI). ALT levels above the 75th percentile were considered increased. Models were adjusted for adjusted for age, sex, waist circumference, BMI, diabetes mellitus, mean daily alcohol consumption and the use of antihypertensive medication. * $P < 0.05$ compared with participants without hyperechogenic liver pattern and without increased ALT levels; linear and logistic regression analyses. ALT, alanine aminotransferase; CI, confidence interval; US, ultrasound.

hyperechogenity and with increased ALT levels showed a higher risk of increased DBP and hypertension.

The results of a multivariable analysis investigating the relation of baseline FLD groups with follow-up BP-related variables in the total sample are depicted in Table 3. Compared to individuals without liver hyperechogenity and without increased ALT levels, those with liver hyperechogenity and with increased ALT levels had a higher risk of increased SBP and hypertension.

Additional analyses were performed after all individuals receiving antihypertensive medication being excluded (Tables 4 and 5). Individuals with liver hyperechogenity and increased ALT levels showed a higher mean SBP and DBP and had a higher risk of increased SBP and DBP and hypertension compared to individuals without liver hyperechogenity and without increased ALT levels at both baseline and follow-up. Individuals without liver hyperechogenity and with increased ALT levels showed a higher risk of hypertension compared to individuals of the reference group at baseline.

As BP shows a diurnal variation, we additionally tested for the influence of time of BP measurement on the association between FLD and BP-related variables and found no substantial changes in our results.

We further performed interaction analyses to investigate whether alcohol consumption modifies the association between FLD and BP-related variables. The interactions between FLD and alcohol consumption with respect to all BP and hypertension-related variables did not attain statistical significance ($P = 0.1–0.9$). Thus, we did not conduct analyses stratified by alcohol consumption.

To evaluate possible bias due to missing data of individuals who did not participate at follow-up examinations, we performed all analyses using weighted data. The associations between FLD and BP-related variables remained stable indicating no bias due to missing data (data not shown).

Discussion

In the present study, we investigated the association between FLD and BP-related variables at baseline and after 5 years using data from a population-based longitudinal study. The main findings of our study are: first, FLD as evidenced by liver hyperechogenity and increased ALT levels was associated with increased DBP and hypertension at baseline and with increased SBP and hypertension at follow-up. Second, in the subgroup of individuals not receiving antihypertensive drugs, FLD was associated with all blood pressure-related variables at baseline and follow-up. Third, alcohol consumption had a minor contribution to the association between FLD and BP-related variables.

Although the associations between FLD and BP-related variables were partly present in the whole study population, our data revealed the most consistent associations in individuals not receiving antihypertensive drugs. BP-lowering effects, which are highly variable across the different antihypertensive substances and dosages, may have biased the analyses in the whole study population resulting in weak and inconsistent associations between FLD and BP-related variables. Therefore, the present findings in the subpopulation taking no antihypertensive drugs strongly confirm our hypothesis

Table 4 Association between fatty liver disease and blood pressure-related variables at baseline in the subgroup of individuals without antihypertensive medication ($n = 2417$)

	US− and ALT− ($N = 1555$)	US− and ALT+ ($N = 285$)	US+ and ALT− ($N = 296$)	US+ and ALT+ ($N = 281$)
SBP, mmHg	129.7 (128.9–130.5)	131.3 (129.3–133.2)	131.6 (129.6–133.6)	133.8 (131.9–135.9)*
DBP, mmHg	81.6 (81.0–82.1)	82.4 (81.2–83.6)	82.5 (81.2–83.7)	85.0 (83.7–86.2)*
Increased SBP (≥140 mmHg)	Ref.	1.3 (0.8–1.7)	1.2 (0.9–1.6)	1.8 (1.3–2.4)*
Increased DBP (≥90 mmHg)	Ref.	1.5 (1.0–2.1)	1.1 (0.8–1.6)	1.7 (1.3–2.4)*
Hypertension	Ref.	1.5 (1.1–2.1)*	1.2 (0.9–1.7)	1.9 (1.3–2.6)*

Data are given as adjusted mean (95% CI) or odds ratio (95% CI). ALT levels above the 75th percentile were considered increased. Models were adjusted for age, sex, waist circumference, BMI, diabetes mellitus and mean daily alcohol consumption. * $P < 0.05$ compared with participants without hyperechogenic liver pattern and without increased ALT levels; linear and logistic regression analyses. ALT, alanine aminotransferase; CI, confidence interval; US, ultrasound.

Table 5 Association between baseline fatty liver disease and blood pressure-related variables at follow-up in the subgroup of individuals without antihypertensive medication ($n = 2417$)

	US− and ALT− ($N = 1555$)	US− and ALT+ ($N = 285$)	US+ and ALT− ($N = 296$)	US+ and ALT+ ($N = 281$)
SBP, mmHg	128.1 (127.2–129.0)	128.7 (126.6–130.7)	127.7 (125.6–129.8)	131.6 (129.5–133.8)*
DBP, mmHg	80.7 (80.2–81.3)	80.7 (79.5–81.9)	80.5 (79.2–81.7)	83.4 (82.1–84.6)*
Increased SBP (≥140 mmHg)	Ref.	1.2 (0.8–1.7)	1.1 (0.8–1.5)	1.7 (1.2–2.4)*
Increased DBP (≥90 mmHg)	Ref.	1.0 (0.7–1.5)	0.9 (0.6–1.4)	1.5 (1.1–2.1)*
Hypertension	Ref.	1.3 (0.9–1.8)	1.1 (0.8–1.6)	1.7 (1.2–2.3)*

Data are given as adjusted mean (95% CI) or odds ratio (95% CI). ALT levels above the 75th percentile were considered increased. Models were adjusted for adjusted for age, sex, waist circumference, BMI, diabetes mellitus and mean daily alcohol consumption. * $P < 0.05$ compared with participants without hyperechogenic liver pattern and without increased ALT levels; linear and logistic regression analyses. ALT, alanine aminotransferase; CI, confidence interval; US, ultrasound.

that FLD represents a risk factor for progression of BP over time and incident hypertension.

We tested for the influence of the diurnal variation of BP on the association between FLD and blood pressure variables. As our analyses revealed almost identical results, it can be assumed that the present findings are not influenced by changes in BP over the day.

We further demonstrated that compared to individuals without liver hyperechogenity or elevated ALT levels, those with liver hyperechogenity and increased ALT levels had a higher BMI and reported higher average daily alcohol consumption. This result indicates that the combination of liver hyperechogenity and increased ALT levels is a hallmark for initiating interventions aimed to reduce BP including weight reduction and alcohol drinking. Although elevated ALT levels are used to detect FLD in routine medical care, the prevalence of FLD might be underestimated due to the low sensitivity of ALT [21]. Our findings emphasize the necessity to implement liver ultrasound in routine medical care to detect FLD if ALT levels are elevated.

Our findings are in good agreement with other longitudinal studies, which demonstrate that FLD is a risk factor for hypertension. For example, Adams and Angulo [13] found that individuals with FLD had higher means for SBP and DBP and higher rates of hypertension at baseline compared to individuals without FLD. Moreover they were more likely to develop hypertension at follow-up. However, this study solely used elevated ALT levels to define FLD. As Palasciano and colleagues [11] point out, blood tests cannot confirm the diagnosis of fatty liver and liver imaging by ultrasound is a sensitive tool in the diagnosis of FLD. The findings of our study are further in line with the results of a case–control cohort study [9], which analysed the development of metabolic disorders in patients with FLD as defined by liver ultrasound. In this study, the incidence of hypertension at the end of follow-up was significantly higher in the FLD group compared to controls. Similar results are reported in a clinical study using data of consecutive patients with FLD. In this study, 28% developed hypertension in the period up to the follow-up examination. Nevertheless, FLD was inconsistently diagnosed using, for example, liver biopsy, ultrasound, computed tomography and laboratory findings [10]. The present study is the first population-based longitudinal study on the association between FLD, BP and hypertension using liver ultrasound and blood testing to detect FLD.

We did not identify any significant interactions between FLD and alcohol consumption with respect to the risk of hypertension. This finding is in line with results from a Chinese population-based study [8]. Cross-sectional data analyses in that study likewise demonstrated that the association between FLD and BP was independent of alcohol consumption. But the prevalence of confirmed alcoholic FLD in this Chinese population was only 0.5% and thereby too low to draw final conclusions on this issue. Also studies on the associations between FLD and other outcomes were independent of alcohol consumption. For example, previous data from SHIP showed that FLD is associated with low insulin-like growth factor-1 levels and that alcohol consumption did not contribute to this association [22]. Other data from SHIP revealed that FLD is associated with serum testosterone and dehydroepiandrosterone sulphate levels in men, and alcohol consumption did also not contribute to these associations [23]. Together with these findings, the results of the present study support the hypothesis that the pathogenesis of FLD is multifactorial and that extrahepatic sequelae of FLD are at least partly independent of the factors that have caused FLD.

We performed all analyses using statistical weights that accounted for dropout from baseline to follow-up. As the associations remained almost identical indicating no bias of relevance due to missing data, it can be assumed that the present results give a reliable estimate of the association between FLD and BP-related variables in the northeast German population.

Our study has several strengths and potential limitations that should be considered. Major strengths of the study encompass the population-based longitudinal design, the large sample size and the ultrasound examinations to detect FLD under strict quality management by standardized protocol and certified staff. Limitations may arise from the inability to perform liver biopsy in a large population-based study like SHIP due to ethical and

logistic concerns, despite the fact that liver biopsy is the best diagnostic instrument to detect FLD.

We conclude that FLD defined by liver hyperechogenity and increased ALT levels is associated with progression of BP over time and incident hypertension. This association is independent of alcohol consumption. In individuals with liver hyperechogenity and increased ALT levels, BP should be checked regularly, and interventions focussing on lifestyle modification including diet, physical activity and alcohol consumption should be initiated. As ALT is determined in routine care, ultrasound should be conducted if ALT levels are elevated.

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There are no conflicts of interest.

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APPENDICES

Appendix A – Eidesstattliche Erklärung

Appendix B – Curriculum Vitae

Appendix C – List of publications

Appendix A – Eidesstattliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät vorgelegt worden.

Ich erkläre, dass ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

Greifswald, den 19.01.2011

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Katharina Lau

Appendix B – Curriculum Vitae

Personal Details

Name:	Katharina Lau
Address:	Gützkower Landstr. 8h, 17489 Greifswald
E-mail address:	katha_lau@yahoo.de
Date of birth:	May 26, 1981
Place of birth:	Magdeburg
Citizenship:	German

Education

1987-1999	Elementary and secondary school education in Magdeburg
2000 - 2006	Otto-von-Guericke University Magdeburg: Education in psychology
2006	Otto-von-Guericke University Magdeburg: Diploma in psychology

Professional experience

2006-2007	Research Fellow at the University of Greifswald, Institute of Epidemiology and Social Medicine (Prof. Dr. U. John)
Since 2007	Research Fellow at the University of Greifswald, Institute for Community Medicine, SHIP/ Clinical-Epidemiological Research Unit (Prof. Dr. Henry Völzke)

Greifswald, January 19, 2011

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Katharina Lau

Appendix C – List of publications

Articles in peer-reviewed journals

Lau, K., Freyer-Adam, J., Coder, B., Riedel, J., Rumpf, H.-J., John, U. and Hapke, U. (2008). Dose-response relation between volume of drinking and alcohol-related diseases in male general hospital inpatients. *Alcohol and Alcoholism, 43(1)*, 34-38.

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Völzke, H., Alte, D., Schmidt, C. O., Radke, D., Lorbeer, R., Friedrich, N., Aumann, N., Lau, K., Piontek, M., Born, G., Havemann, C., Ittermann, T., Schipf, S., Haring, R., Baumeister, S. E., Wallaschofski, H., Nauck, M., Frick, S., Arnold, A., Jünger, M., Mayerle, J., Kraft, M., Lerch, M. M., Dörr, M., Reffelmann, T., Empen, K., Felix, S. B., Obst, A., Koch, B., Gläser, S., Ewert, R., Fietze, I., Penzel, T., Dören, M., Rathmann, W., Haerting, J., Hannemann, M., Röpcke, J., Schminke, U., Jürgens, C., Tost, F., Rettig, R., Kors, J. A., Ungerer, S., Hegenscheid, K., Kühn, J. P., Kühn, J., Hosten, N., Puls, R., Henke, J., Gloger, O., Teumer, A., Homuth, G., Völker, U., Schwahn, C., Holtfreter, B., Polzer, I., Kohlmann, T., Grabe, H. J., Rosskopf, D., Kroemer, H. K., Kocher, T., Biffar, R., John, U. and Hoffmann, W. (2010). Cohort Profile: The Study of Health in Pomerania. *International Journal of Epidemiology* (doi:10.1093/ije/dyp394).

Schipf, S., Haring, R., Friedrich, N., Nauck, M., Lau, K., Alte, D., Stang, A., Völzke, H. and Wallaschofski, H. (in press). Low Total Testosterone is Associated with Increased Risk of Incident Type 2 Diabetes Mellitus in Men: Results from the Study of Health in Pomerania (SHIP). *The Aging Male.*

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Lau, K., Schmidt, C.O., Lorbeer, R., Haring, R., Baumeister, S.E., Mayerle, J., Wallaschofski, H., Dörr, M., Felix, S.B. and Völzke, H. Fatty liver disease, blood pressure, and left ventricular mass: Results from a prospective cohort of 45 to 81-year old individuals.

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Lau, K., Freyer-Adam, J., Coder, B., Riedel, J., Rumpf, H.-J., John, U. and Hapke, U. (2007). *Dosis-Wirkungs-Zusammenhang zwischen Alkoholkonsum und alkoholbezogenen Erkrankungen bei männlichen Krankenhauspatienten*. Augsburg: Kongress Medizin und Gesellschaft.

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Lau, Katharina (2008). Elterliche Erziehung und Eltern-Kind-Beziehung. Saarbrücken: vdm.

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Lau, K., Lorbeer, R., Haring, R, Schmidt, C.O., Wallaschofski, H., Nauck, M., John, U., Baumeister, S.E. and Völzke, H. (2010). The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study. Berlin: Kongress Medizin und Gesellschaft.

Poster presentations (first author)

Lau, K., Coder, B., Pockrandt, C., Hartmann, B., John, U. and Freyer-Adam, J. (2007). *Health behaviors and health risk behaviors among job-seekers: Testing the suitability of employment agencies for prevention.* Greifswald: 3. Tagung der Suchtforschungsverbünde des Bundesministeriums für Bildung und Forschung.

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