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LIGHT TO MODERATE ALCOHOL CONSUMPTION AND ACUTE MYOCARDIAL INFARCTION, HEART FAILURE AND ATRIAL FIBRILLATION

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Light to moderate alcohol consumption and acute myocardial infarction, heart failure and atrial fibrillation

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background and aim: A large number of studies found an inverse association between light to moderate alcohol consumption and the risk of acute myocardial infarction (AMI) and heart failure (HF). Whether this consumption is associated with the risk of atrial fibrillation (AF) is less clear. Methodological shortcomings may limit causal inference in these studies, most importantly the “sick-quitter” bias and the confounding by social factors. Furthermore, how drinking frequency, binge- and problem drinking or beverage types may influence these associations is not well understood. The overall aim of this thesis is to contribute to a better understanding of the prospective associations between light-to-moderate alcohol intake and the risk of AMI, HF and AF by addressing the above described unresolved issues.

Methods and results: The Nord-Trøndelag Health Study (HUNT) is a large Norwegian population-based study conducted in three waves. For study I and II, we used data from HUNT2 conducted in 1995 -1997. In HUNT2, 65 215 individuals (70% of the eligible) participated and were followed for AMI and HF. For study III and IV, HUNT3 conducted in 2006-2008, was used: 50 807 individuals (54% of the eligible) participated and were followed for AF. In study III, 1 266 healthy individuals were selected randomly from HUNT3 and had an echocardiography examination.

The quantity, type and frequency of alcohol consumption were ascertained by questionnaires. Binge drinking, i.e. drinking \geq five glasses in one sitting and problem drinking were assessed. To identify abstainers who were former drinkers, information from the preceding waves of HUNT, i.e. HUNT1 or HUNT2 were used. They were categorized as long-term abstainers, abstainers who were former drinkers, rare drinkers, and drinkers, who were further categorized based on average alcohol consumption in a two-week period. Information on socioeconomic position, demographics, smoking, physical activity, common chronic conditions, and anxiety and depression symptoms were assessed, and anthropometrics, blood pressure and blood lipids were measured.

The average alcohol consumption in the HUNT was 3-4 grams per day. The quantity of alcohol consumption was inversely associated with the risk of AMI and HF (study I, II). There was no clinically meaningful association between light to moderate alcohol intake and LV function (study III). Compared to abstainers, drinkers who consumed over seven drinks per week had an increased risk of AF. However, when we excluded those who consumed alcohol over the recommended limits, i.e., $>$ seven drinks per week for women and >14 drinks per week for men and reported binge and/or problem drinking the attributable risk of alcohol consumption was negligible in this low-drinking population (study IV). Frequent, more evenly distributed alcohol consumption was more protective for AMI and HF than less frequent intake of the same quantity (study I, II). Among binge and/or problem drinkers, alcohol consumption was associated with a slightly increased risk of HF and worse LV structural characteristics (study II, III).

Conclusions: Light to moderate alcohol consumption, within the recommended limits was associated with a reduced risk of AMI and HF, but not with the risk of AF. While frequent low-level consumption is associated with the lowest risk of AMI and HF, binge drinking seems to be harmful even if the average alcohol intake is moderate. Alcohol consumption within the recommended limits may provide some cardiovascular benefits without increasing the risk of AF.

LIST OF SCIENTIFIC PAPERS

- I. K GÈMES, I Janszky, LE Laugsand, KD László, S Ahnve, LJ Vatten, KJ Mukamal. Alcohol consumption is associated with a lower incidence of acute myocardial infarction: results from a large prospective population-based study in Norway. *J Intern Med*. 2016 Apr;279(4):365-75.
- II. K GÈMES, I Janszky, S Ahnve, KD László, LE Laugsand, LJ Vatten, KJ Mukamal. Light-to-moderate drinking and incident heart failure - the Norwegian HUNT study. *Int J Cardiol*. 2016 Jan 15;203:553-60
- III. K GÈMES, I Janszky, LB Strand, KD László, S Ahnve, LJ Vatten, H Dalen, KJ Mukamal. Light-moderate alcohol consumption and left ventricular function among healthy, middle aged adults – the HUNT study. Submitted
- IV. K GÈMES, V Malmo, LE Laugsand, JP Loennechen, H Ellekjær, KD László, S Ahnve, LJ Vatten, KJ Mukamal, I Janszky. Does moderate drinking increase the risk of atrial fibrillation? The Norwegian HUNT study. *The Journal of American Heart Association*, accepted.

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LIST OF ABBREVIATIONS

AMI	Acute myocardial infarction
HF	Heart failure
AF	Atrial fibrillation
ECG	Electrocardiogram
ICD	International Classification of Diseases
CVD	Cardiovascular diseases
IHD	Ischemic heart diseases
HR	Hazard ratio
CI	Confidence interval
HDL	High density lipoprotein
LDL	Low density lipoprotein
HUNT	Helseundersøkelsen i Nord-Trøndelag (Nord-Trøndelag Health Study)
g	Gramm, metric unit of mass

1 BACKGROUND

Alcohol consumption is culturally and economically integrated into many societies. There is a vast public health interest in its effect on health. Heavy drinking, i.e., consuming on average above 60 g of alcohol for men and 40 g of alcohol per day for women [1], is apparently one of the major avoidable risk factors for several health outcomes and is responsible for 3.8% of deaths and for 4.6% of disability-adjusted life-years lost globally [2-4]. It is associated with an increased risk of injuries, infectious diseases, cirrhosis, several types of cancer, diabetes, dementia and neuropsychiatric diseases [1]. Heavy drinking during pregnancy is associated with an increased risk of foetal alcohol syndrome and several other adverse birth outcomes [1, 5]. Compelling evidence shows that individuals with alcohol use disorders have an increased risk of several adverse cardiovascular outcomes [3, 6-10], primarily cardiac arrhythmias, heart failure (HF) and stroke [11-15]. Heavy drinking has a clear cardio-toxic effect and may induce cardiomyopathy [3, 14, 16].

On the other hand light to moderate alcohol consumption is associated with a lower risk of overall mortality and several common chronic diseases [17, 18]. Studies have reported a reduced risk of type-2 diabetes [19-21], dementia, Alzheimer disease [22, 23] and cardiovascular diseases (CVD) [10, 12, 13, 18, 24-26] among individuals consuming on average 10-40 g of alcohol per day compared to non-drinkers. According to the Global Burden of Alcohol Study, the maximal protection associated with alcohol consumption is around 6-10 g per day on average for both sexes [17]. The reversion point, where the net benefit equals its harm is at 10-20 g per day for women and at 35-40 g per day for men, which roughly corresponds to 1-2 and 3-4 drinks per day of average alcohol intake, respectively [17]. Other studies found that this turning point was at a slightly higher consumption level, at around 40 g per day in women and at around 60 g per day in men [1, 25].

The possible protective association between alcohol intake and the risk of CVD was first described in ecological studies that found lower cardiac mortality rates in countries where regular wine consumption is widespread [27]. The “French paradox” refers to the related phenomenon that in France, a country with a long tradition of drinking wine, the linear relationship between dietary fat intake and CVD, described in other countries could only be found after the adjustment for alcohol consumption. Since then, a large number of studies with individual-level data have been conducted to examine the association between alcohol consumption and CVD. Compelling evidence now shows that a light to moderate level of alcohol intake, approximately 10 to 40 g per day, is inversely associated with the risk of ischemic heart diseases (IHD) [12, 13, 24, 28, 29], HF [8, 30], cerebrovascular diseases [9, 12] and peripheral arterial disease [10, 25, 26]. However, whether this association is causal, and what are the exact public health implications of these findings remain unclear due to a number of methodological problems in previous research. At the same time, the knowledge regarding the association between light to moderate alcohol consumption and some specific

CVD, most importantly atrial fibrillation (AF) and other supraventricular cardiac arrhythmias [7, 31, 32] is still limited.

Cardiovascular diseases are the major causes of death and disability worldwide, as approximately 30% of global deaths are attributable to CVD [33]. In Europe, 45% of all deaths in 2016 were due to CVD, and more than 30% of these occurred under the age of 75 [34]. A better knowledge of the effect of light to moderate alcohol consumption on CVD is of a great public health importance. Therefore, the focus of this thesis is to contribute to a better understanding of the associations between light to moderate alcohol consumption and the risk of AMI, HF and AF, using a large population-based study to account for some of the limitations of previous research. First, cardiovascular outcomes and their underlying pathology are described, followed by previous research regarding the association of light to moderate alcohol intake with each of these outcomes. Finally, the major methodological challenges of previous research are presented.

1.1 CARDIOVASCULAR DISEASES INVESTIGATED IN THIS THESIS

1.1.1 Acute myocardial infarction

Acute myocardial infarction (AMI), a clinical expression of IHD, is one of the major contributors to the burden of diseases worldwide [35-37]. According to the Swedish National Board of Health and Welfare, in 2015, approximately 26,600 individuals had an AMI in Sweden (www.socialstyrelsen.se). Acute myocardial infarction occurs when the blood supply in coronary arteries is insufficient; which leads to localised ischemia in the heart muscle [37]. The diagnosis of AMI is based on the presence of symptoms such as chest pain, dyspnea, unexplained weakness and nausea, specific ECG changes and elevated cardiac enzyme levels [37].

The underlying pathology of AMI is atherosclerosis for most cases. Atherosclerosis is a multifactorial disease of the arteries that causes a thickening and hardening of the endothelium and loss of elasticity of the arteries [38]. During the development of atherosclerosis, an initially physiologically adaptive and reversible thickening of the intima becomes a pathological process that results in fat accumulation in the endothelium and the development of atherosclerotic plaques [38, 39]. Atherosclerosis is considered an inflammatory disease, as low-grade chronic inflammation mediates all of its stages including initiation, plaque formation and thrombotic complications [39]. Disturbed cellular and endothelial expression of different adhesion molecules, the production of inflammatory cytokines and the oxidation of low-density lipoprotein (LDL) cholesterol play an essential role in triggering and maintaining inflammation in the endothelium [39-42]. Acute myocardial infarction often develops due to an atherosclerotic plaque rupture or erosion, when the thrombogenic material from the atherosclerotic plaque may occlude the coronary arteries [37, 41-43].

1.1.2 Heart failure and left ventricular dysfunction

Heart failure is a complex clinical syndrome which occurs when the pump function of the heart is impaired due to structural or functional cardiac impairments or injuries [44]. It may cause symptoms like swelling of the limbs, fatigue, increased breathing difficulties and exertion during physical activity [44, 45].

The clinical diagnosis of HF is based on the presence of these symptoms, as well as on structural and functional changes of the heart observed with echocardiography and elevated natriuretic peptide levels [44]. HF affects approximately 26 million individuals worldwide. It is one of the leading reasons for hospitalisation in the Western world and causes huge healthcare expenditures [46, 47]. In Sweden, the estimated prevalence is 2.2% and the incidence is 3.8 per 1000 person-years [48]. It is especially frequent among those over 70 years of age and is associated with high mortality and morbidity [44, 46].

The pathophysiology of HF often involves myocardial injury that alters the loading and the biochemical environment of the myocytes, which results in disturbed biochemical signalling. This further results in cardiac remodelling and might later lead to left ventricular (LV) systolic and/or diastolic dysfunction and decreased cardiac output. Besides the functional and structural dysfunction of the myocardium, valvular diseases, peri- and endocardium anomalies, cardio-myopathies due to genetics or cardio-toxic agents as well as arrhythmias may also contribute to HF development [44].

Heart failure diagnoses include clinical symptoms that may be apparent, but asymptomatic LV functional and structural dysfunctions, which are strong precursors of HF can be detected by echocardiography before the first symptoms appear [44]. While a dilated LV wall and decreased ejection fraction are straightforward signs of functional impairment, in many cases the ejection fraction is largely preserved [44]. However, increased LV wall thickness, LV mass and/or left arterial size with subtle echocardiographic anomalies in systolic functional indices can be signs of cardiac functional and structural alterations of the myocardium [44].

1.1.3 Atrial fibrillation

Atrial fibrillation is the most common symptomatic cardiac arrhythmia [49, 50]. It usually manifests in rapid, irregular heartbeats, fluttering in the chest, palpitation, tiredness or shortness of breath, but it may also be 'silent' with no noticeable symptoms [49]. The diagnosis is primarily based on ECG recordings [49]. Atrial fibrillation affects 2-3% of the adult population in Europe and its incidence and prevalence are increasing [51, 52]. Most AFs are considered to be chronic conditions and require life-long treatment [49], and it increases overall mortality and morbidity [49, 50, 53, 54], as it is a strong risk factor for stroke and HF [49].

The primary underlying pathophysiological mechanisms in AF involve the structural and functional changes of the atrial wall, so-called atrial remodelling [55]. Atrial remodelling increases the likelihood of spontaneous arrhythmogenic mechanisms and susceptibility to external arrhythmogenic triggers such as heavy alcohol consumption [32, 55].

1.2 PREVIOUS RESEARCH ON ALCOHOL CONSUMPTION AND THE RISK OF AMI, HF AND AF

1.2.1 Alcohol consumption and the risk of IHD, AMI, HF and AF

Compelling evidence suggests that the association between the quantity of alcohol consumption and IHD has a J or U shape, i.e., light to moderate alcohol intake is associated with lower IHD risk compared to abstinence, while heavy drinking and alcohol use disorder is associated with an increased risk of IHD [12, 13, 24-26]. According to a meta-analysis from 2012, light to moderate alcohol intake, or 10-40 g per day on average, is associated with a 20-40% lower risk of IHD compared to non-drinking [24]. The amount of alcohol intake where the risk of IHD starts to increase in comparison with zero alcohol consumption is around 50-70 g per day [12, 24, 26].

Heavy drinking is a well-established risk factor for HF. Alcoholic cardiomyopathy is a relatively frequent condition among heavy drinkers that often leads to LV dysfunction through the direct toxic effect of alcohol on the myocytes [14, 16, 56-58]. Heavy alcohol consumption may cause cardiac fibrosis that can alter LV function [59]. However, persons consuming up to 14 drinks per week seem to have an approximately 20% lower risk of HF compared to non-drinkers [8, 15, 30, 60]. As IHD contributes the most to the aetiology of HF, it is not clear whether the observed protective association between light to moderate alcohol intake and HF is mediated through its protective effect on IHD, or whether other biological mechanisms play a role as well [8, 30]. Studies that examine HF with ischemic and non-ischemic aetiology separately only show the protective effect of light to moderate alcohol intake among ischemic HF cases [61]. The results are mixed with regard to light to moderate alcohol intake and LV function. Studies find better [58], or worse LV functional and structural characteristics [62], or no clinically relevant differences in LV function among those consuming up to 14 drinks per week compared to non-drinkers [63, 64].

Heavy alcohol consumption and alcohol use disorder are also associated with an increased risk of AF [7, 32, 65, 66]. Heavy alcohol intake influences the electrophysiological properties of the cardiomyocytes [32] and may cause electromechanical delay and increased sympathetic activity [32, 66-68]. However, it is unclear whether light to moderate alcohol consumption is associated with an increased risk of AF and whether there is a safe limit of alcohol intake up to which there is no meaningful AF risk increase [32]. While some suggest that alcohol intake is linearly associated with AF risk [69], others hypothesize that the association is curvilinear, i.e. that there is no increased risk up to a certain amount but a steeper increase in risk above a specific threshold [7, 31, 32, 70].

1.2.2 Drinking frequency and binge drinking

The majority of previous studies assessed only the quantity of alcohol intake. However, the pattern of alcohol consumption might modify the association between the amount of alcohol consumption and CVD risk. Binge drinking, generally defined as consuming ≥ 4 drinks for women and ≥ 5 drinks for men in one single occasion at least once a month [71-73], is

harmful for cardiovascular health [28, 74, 75]. Studies show that a binge episode can increase the risk of acute coronary syndromes [29, 76] and supraventricular tachycardia within the first 24 hours after heavy alcohol consumption [1, 77]. This triggering effect of binge drinking on supraventricular tachycardia has been traditionally referred to as the “holiday heart symptom” [65]. Experimental studies found that acute alcohol infusion increases sympathetic nervous system activity, blood pressure and prothrombotic activity [28, 75, 76]. The increased release of catecholamines might trigger arrhythmias [57], and can directly damage the myocytes by inducing oxidative stress [57, 59, 78-80]. Binge drinking may alter the favourable association between alcohol consumption and IHD and HF even among moderate drinkers, consuming an average of 7-14 drinks per week [1, 25, 81]. It is also possible that the observed increase in AF among individuals, consuming within the recommended levels, at most 7 drinks per week for women and 14 drinks per week for men [82-84], may be due to the increased risk attributed to binge drinking.

Studies show that evenly distributed frequent alcohol intake is associated with a more favourable IHD risk than less frequent intake of the same quantity [1, 25, 81]. Among drinkers consuming 7-14 drinks per week, those who report lower drinking frequency, consume a larger amount of alcohol on drinking days [85]. While the role of drinking frequency has been examined in relation to IHD, no previous study has investigated this in relation to HF or AF.

1.2.3 Beverage type

Whether the association between light to moderate alcohol intake and CVD differs according to beverage type is unclear, as well as whether the possible protective effects can be explained by alcohol itself or by other components of alcoholic beverages. Observational research concerning the effect of different beverage types on IHD risk yielded conflicting results. While some studies found a greater benefit among wine and beer drinkers compared to spirit drinkers [86-88], meta-analyses could not confirm that polyphenol-rich alcoholic beverages have a more positive effect [18]. In vitro biological studies show that polyphenols in wine have strong antithrombotic and antioxidant properties and also suppress inflammation [89-93]. Even alcohol-free wine stimulates antioxidant enzymes in human [94]. Polyphenols also modulate leukocyte adhesion molecules and improve gut microbiome [88, 91, 93]. However, the bioavailability of polyphenols in human is poor and only a small amount of the polyphenols in wine stay in active form and get into the bloodstream [92, 95, 96]. The examined favourable effect of wine might also be partly due to residual confounding. Wine drinkers usually have better education and health, have more favourable health-related behavioural patterns, and are more likely to follow a healthier drinking pattern than spirit drinkers. This may explain why previous findings are inconsistent concerning possible beverage-specific effects on CVD [97].

1.2.4 Methodological challenges

There is compelling evidence in support of the biological plausibility of the potential protective effect of light to moderate alcohol intake on atherosclerotic CVD; this includes increased HDL cholesterol level [88, 96, 98, 99], decreased inflammation [18, 88, 91, 100], decreased thrombotic activity [18, 101] and improved glycaemic control [93, 102-104] among other mechanisms. Nevertheless, there are no randomised controlled trials on light to moderate alcohol and risk of CVD as there are major ethical considerations against such a trial. The best evidence concerning this research question comes from observational studies, but there are several methodological considerations in relation to the results of these studies. While some of them are general concerns that can potentially affect all observational studies, others are more specific to this research field. In this thesis, we focus on the latter ones.

1.2.4.1 *Choice of reference group*

One of the most frequently discussed methodological aspects related to the inverse association between light to moderate alcohol consumption and CVD risk is related to the abstainer group [10]. In most Western countries the abstainer or non-drinker group is a mixed group which contains long-term abstainers and former heavy drinkers who stopped due to ill-health [10, 105]. Abstinence from alcohol at baseline may be the consequence of a worsening health during the previous years, and the observed increased risk of these non-drinkers is due to their ill-health. The inclusion of abstainers who were former drinkers can bias the estimates considerably and this is often referred to as the “sick quitters bias” [105, 106]. Several studies have tried to reduce this problem by distinguishing between long-term abstainers and abstainers who were former drinkers. The simplest assessment of previous drinking habits is to ascertain it at baseline measurement; however, this is problematic as retrospective recall of previous alcohol consumption may not be accurate. As such, few studies have been able to assess alcohol consumption habits longitudinally and separate long-term abstainers and abstainers who were previous drinkers based on assessments prior to the baseline.

1.2.4.2 *Confounding due to cultural and social norms regarding alcohol consumption*

Moderate alcohol consumption is the socially accepted norm in many Western countries. Light to moderate drinkers are on average more educated, have higher income, better general health, fewer chronic conditions and better CVD risk profiles than abstainers and heavy drinkers [18, 97]. They also have better social support, are more socially active and have better mental health than abstainers [97]. Long-term abstainers are often a very specific group, that might differ ethnically and culturally from rare- and light to moderate drinkers [25, 85, 107, 108]. There could be further characteristics that might differ between abstainers and light to moderate drinkers which are difficult to take into account. Therefore, residual confounding due to the unmeasured factors in these studies might lead to an overestimation of the possible protective effects of light to moderate alcohol intake on CVD [18]. On the other hand, light to moderate drinkers are more likely to be smokers than abstainers, and incomplete control of smoking habits may, in theory, lead to an underestimation of the protective effect. As the information on confounders is limited in traditional cohort studies,

some studies have used Mendelian randomisation to overcome this problem; in these studies genetic polymorphism is considered an instrumental variable for alcohol consumption [109]. However, the results of these studies varied, according to the chosen genetic polymorphisms [110, 111], which may indicate that some of the assumptions behind this method might have been violated. Unfortunately, these assumptions are difficult and sometimes impossible to evaluate [109]. Twin studies, which could control for shared genetic and environmental factors, confirmed the protective association between light to moderate alcohol intake and IHD risk [112].

2 AIMS OF THE THESIS

The overarching aim of this thesis is to contribute to a better understanding of the associations between light to moderate alcohol intake and AMI, HF and AF by addressing the major methodological shortcomings in previous research, by using a large population-based cohort in Norway. The majority of the cohort participants were non- or very light drinkers, as non-drinking is more culturally acceptable in Norway than in other Western countries. As the population was surveyed three times during ten years, we had the opportunity to consider former alcohol consumption habits.

The specific research questions are:

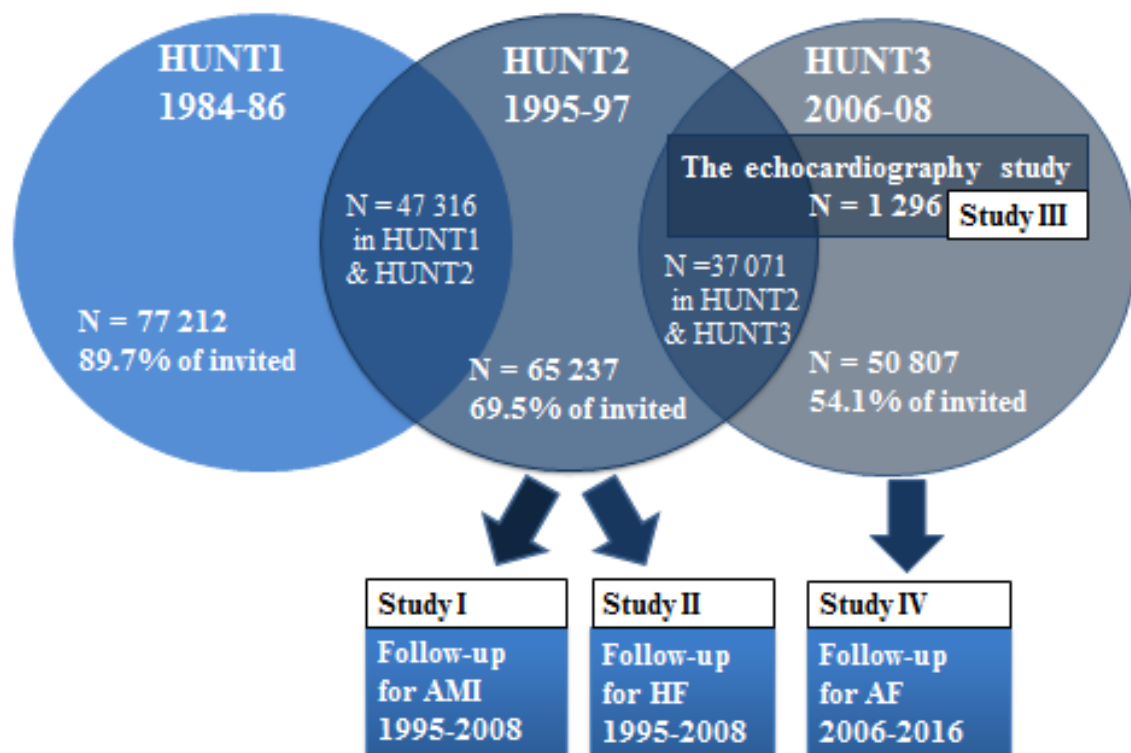
1. Is light to moderate alcohol consumption associated with a lower risk of AMI? (Study I)
2. Is light to moderate alcohol consumption associated with a lower risk of HF, and if so to what extent is this association explained by AMI? (Study II)
3. Does drinking frequency or beverage type modify the association between alcohol consumption and AMI and HF, respectively? (Studies I and II)
4. Is light to moderate alcohol consumption associated with a better LV function? How does binge drinking influence the association between alcohol intake and LV function? (Study III)
5. Is light to moderate alcohol consumption associated with an increased risk of AF? Is alcohol consumption within the recommended limits still associated with an increased risk of AF? (Study IV)

3 MATERIALS AND METHODS

3.1 STUDY POPULATION

The HUNT study is a population-based cohort study that was conducted in three waves. (<http://www.ntnu.edu/hunt>). The first wave of HUNT (HUNT1) was conducted between 1984 and 1986, the second wave (HUNT2) between 1995 and 1997 and the third wave (HUNT3) between 2006 and 2008 (Figure 1). On all three occasions, the whole adult population (aged above 20 years) of the Nord-Trøndelag County in central Norway was invited to participate. The first questionnaire and an information pamphlet for written consent were sent out to each individual. The studies were approved by the regional committee of ethics in medical research, the National Directorate of Health and the Norwegian Data Inspectorate [113].

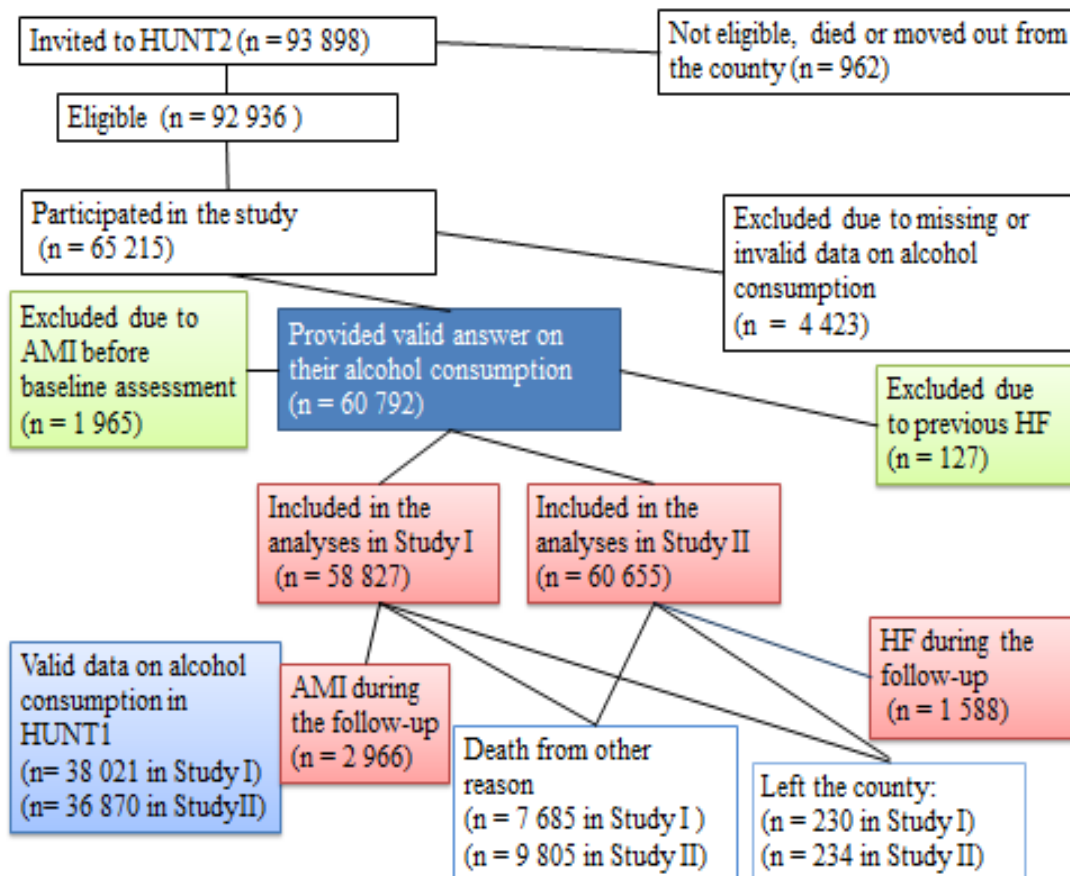
Figure1. The HUNT studies and follow-up for the studies included in the thesis



3.1.1 HUNT2 (studies I and II)

A total of 93 898 persons were invited to the second wave of the HUNT study, of which 65 215 individuals participated. They completed questionnaires regarding their socio-demographic characteristics, health status, quality of life, chronic illnesses, and health behaviour. In the study centres, a standardised clinical examination was conducted by trained nurses, which included standard anthropometric measurements such as height, weight, hip and waist circumference, and blood pressure assessment. Blood and saliva samples were also taken [113]. All individuals participating in HUNT2 who had valid alcohol information and had no previous AMI were included in study I (n=58 827). Individuals with valid alcohol information and without previous HF were included in study II (n= 60 655) (Figure 2).

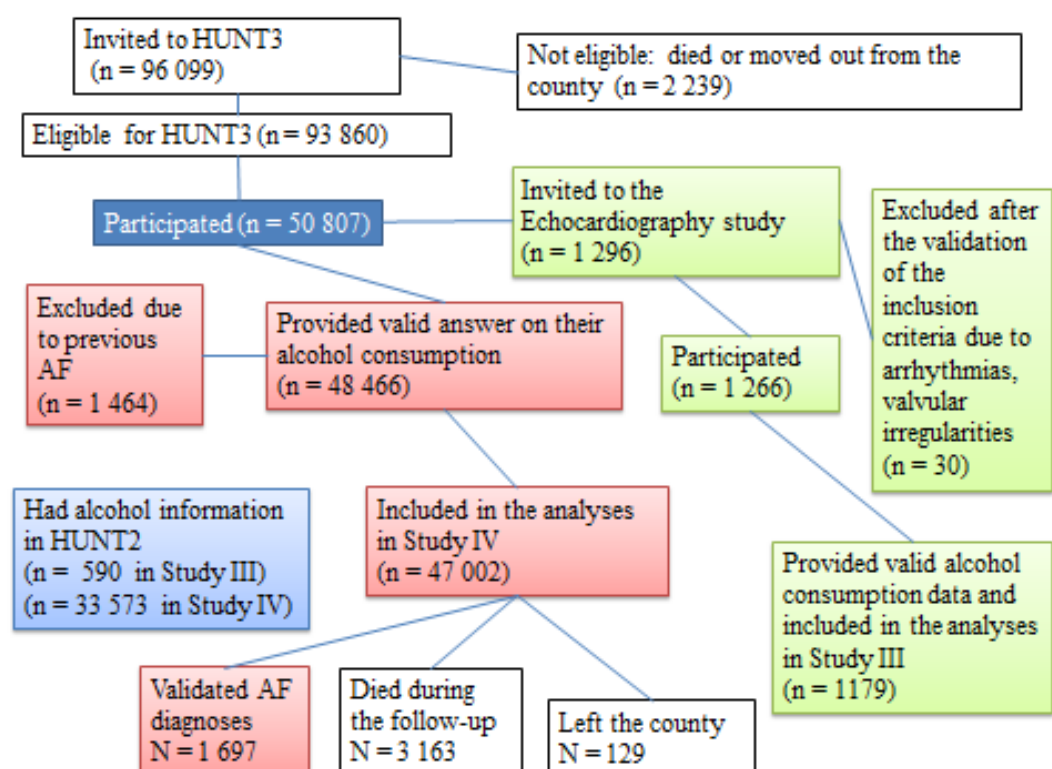
Figure 2 Selection of study participants for studies I and II



3.1.2 HUNT3 (study IV)

Altogether 93 860 adult residents of the Nord-Trøndelag County were invited to HUNT3 and, 54.1% of them participated (Figure 3). As in HUNT2, data on sociodemographic factors, self-reported health, chronic health conditions, and health-related behaviours were collected by self-reported questionnaires. The same anthropometric and clinical measurements were assessed as in HUNT2, and blood and saliva samples were taken at the study centres. In study IV, we included 47 002 participants from HUNT3, who were free of previous AF and who provided valid answers concerning their alcohol consumption.

Figure 3. Selection of study participants in studies III and IV



3.1.3 The echocardiography study (study III)

A subsample of healthy individuals, (n=1 296) without known CVD, diabetes or hypertension was randomly selected from the HUNT3 cohort [114, 115] and underwent tissue Doppler and greyscale speckle tracking echocardiography. The inclusion criteria were validated by an experienced physician, and altogether 30 participants were excluded due to arrhythmias, myocardial or valvular pathology [114, 115]. In addition, for the current study, we excluded participants who did not provide valid data on alcohol consumption, resulting in 1 179 participants included in study III (Figure 3).

3.2 STUDY VARIABLES

3.2.1 Measures of alcohol consumption

In HUNT2 (studies I and II) alcohol consumption was measured with the following questions: (<https://www.ntnu.edu/hunt/data/que>):

- “Concerning alcohol, are you a non-drinker?”
- “How many times a month do you normally drink alcohol?” not including low-alcoholic beer, that contains less than 3.5% alcohol.
- “How many glasses of beer (containing more than 3.5% alcohol by volume), wine or spirits do you usually drink in the course of two weeks”.

Those who answered “yes”, or did not answer the first question but reported zero alcohol consumption on the third question were considered abstainers. Those who did not consider themselves non-drinkers, but reported zero alcohol consumption on the third question were categorized as rare-drinkers, i.e. consuming less than one drink in a usual two week period (or <0.5 drinks per week). Those who reported a minimum of one drink alcohol consumption during a usual two week period were categorised according to the *amount of alcohol consumption*: (i) ≥ 0.5 and ≤ 2.5 , (ii) > 2.5 and ≤ 5 , (iii) > 5 and ≤ 7 and (iv) > 7 drinks per week. Daily alcohol consumption was also calculated using an average of 12 g alcohol per drinks [17].

The *frequency of alcohol consumption* was categorised based on the answer to the second question as: (i) less than once a month (abstainers and rare-drinkers), (ii) on one to four occasions in a month, (iii) on five or more occasions per month in study II. In study I, drinkers were categorized similarly except that the upper category was further classified as (iii) on five to 12 occasions and (iv) on more than 12 occasions.

In HUNT3 (studies III and IV) the amount and the frequency of alcohol consumption were measured with the following three questions (<https://www.ntnu.edu/hunt/data/que>):

- “About how often in the last 12 months did you drink alcohol?”
- “Did you drink alcohol during the last 4 weeks?”
- “How many glasses of beer (containing more than 3.5% alcohol by volume), wine or spirit do you usually drink in a course of two weeks?”

In studies III and IV, participants were categorised according to the quantity of alcohol consumption as: (i) abstainers who reported no alcohol consumption during the last year, (ii) rare drinkers, who reported no alcohol consumption for a usual two week period, but answered that they consumed alcohol at least once in the last 12 months and/or during the last four weeks. Those who reported any alcohol consumption in a usual two week period were categorised as (iii) consuming at most three drinks, (iv) more than three, but at most seven drinks and (v) more than seven drinks during a week. Daily alcohol consumption was calculated as in previous studies, assuming 12 g alcohol in one standard drink [3, 25, 116].

The frequency of alcohol consumption was categorised as: (i) less than once a month, (ii) one to four times a month or (iii) more than once a week.

Problem drinking (studies I-IV) was assessed by the CAGE questionnaire (the acronym stands for cut down, annoyed, guilty and eye-opener) [113], which is a short problem drinking screening instrument [117], and contains the following four items: “Have you ever felt that you should *cut down* your alcohol intake?”; “Have other people *annoyed you* by ever criticizing your use of alcohol?”; “Have you ever felt bad or *guilty* because of your use of alcohol?”, “Have you ever had a drink first thing in the morning as a pick-me-up or to calm your nerves or to cure a hangover (*eye-opener*)?”. For all four questions, the respondents could answer either “yes” or “no”. According to a validation study in HUNT, at least two affirmative answers on the four questions have high specificity for detecting problem drinking behaviour [118].

Binge drinking (studies III and IV) was assessed only in HUNT3. The question: “How often do you drink 5 glasses or more of beer, wine or spirits in one setting” was used. Those who answered monthly, weekly or daily (in study III) and weekly or daily (in study IV) were considered binge drinkers.

Risky drinking (studies III and IV) was defined based on a report of either binge drinking and/or at least two affirmatory answers on the CAGE questionnaire.

Previous alcohol consumption and categorisation of abstainer: In study I and II information on previous alcohol consumption could be obtained from HUNT1 for a substantial proportion of HUNT2 participants. In HUNT1 participants were asked about how often they drank alcohol in the past two weeks. They could choose from the following answers: (i) did not drink alcohol, although not an abstainer, (ii) drank alcohol one or four times, (iii) drank alcohol five to 10

times, (iv) drank alcohol more than 10 times, or (v) abstainer. According to the answers given, abstainers in HUNT2 were further categorized as *long-term abstainers*, if they were abstainers or reported no alcohol consumption in HUNT1 and *abstainers, who were former drinkers* if they reported alcohol consumption at HUNT1. For Study III and IV, previous alcohol consumption was obtained from the HUNT2 questionnaire. Participants who gave valid answers to the alcohol-related questions in HUNT2 were categorised as drinkers if they reported at least one alcoholic drink during a regular two week period or non-drinkers if they reported no alcohol consumption during a regular two week period. Abstainers from HUNT3 were categorized similarly as (i) *long-term abstainers* if they were non-drinkers in HUNT2, and (ii) *abstainers, who were former drinkers*, if they reported any alcohol consumption in HUNT2.

3.2.2 Outcome information

In study I and II the HUNT2 population was followed for incident AMI and HF, respectively. In study IV the HUNT3 population was followed for incident AF. In all three studies cases were identified from the medical records of the two regional hospitals of Nord-Trøndelag County and for study I and II also from the National Cause of Death Register.

3.2.2.1 Acute Myocardial Infarction (study I and II)

Participants were followed for AMI until December 31st, 2008. To identify AMIs the diagnostic criteria of the European Society of Cardiology/American College of Cardiology consensus guideline was used [119]. The diagnoses of AMI were based on experiencing specific symptoms, changes in the blood level of specific enzymes and specific changes in ECG. Cases that did not reach the hospitals were identified from the National Cause of Death Register using the ICD-9 code 410 and the ICD-10 codes I21 and I22. The AMI was defined as fatal if the patient died within the first 28 days, and non-fatal if the patient survived the first 28 days. Previous AMI cases were identified by searching for diagnoses in the five years prior to the baseline measurement in the medical records as well as from the HUNT2 questionnaire with the question “Have you ever been diagnosed with AMI?”.

3.2.2.2 Heart Failure (study II)

Participants were followed for HF until December 31, 2008. The diagnoses of HF were based on the Guideline of the European Society of Cardiology and included symptoms and signs of HF and evidence of cardiac dysfunction [45]. Cases that did not reach the hospital were identified from the National Cause of Death Register using the ICD-9 code: 428 and the ICD-10 codes 150.0, 150.1 and, 150.9. Previous HF cases were identified by searching for HF diagnoses in the 5 years prior to the baseline measurement in the hospital discharge records.

3.2.2.3 Left ventricular functional and structural indices

The echocardiography measurements were conducted by an experienced medical professional according to the American Society of Echocardiography and European Society of

Echocardiography recommendations [120]. The echocardiography was assessed in a left-lateral decubitus position using a Vivid 7 scanner (version BT06, GE Ultrasound, Horten, Norway) with a phased-array transducer (M3S and M4S). The echo-Doppler examination was conducted in the parasternal long-, short-axis views and in three standard apical views. In each orientation, at least three consecutive cardiac cycles were recorded and the functional indices were calculated using the average specific values of the three cycles. From the three apical planes, separate greyscale and colour tissue Doppler imaging were recorded. Systolic mitral annular excursions (MAE) were acquired from the base of the inferoseptal, anterolateral, inferior and anterior wall. Peak systolic (S') and peak early diastolic mitral annular velocity (e') were calculated as the average of the peak velocities measured at the same locations by pulsed-wave tissue Doppler echocardiography [120]. Tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic velocity (RS') were measured close to the tricuspid plane in the free wall of the right ventricle. Global longitudinal end-systolic strain (the percentage of LV shortening during the systole) and peak global strain rate (the maximum speed of the global longitudinal strain) were measured as the average of the segmental values based on the 16 segments model of the LV. Mitral inflow early (E) and late (A) diastolic velocities were recorded by pulse wave Doppler, and the E/A ratio was calculated. E/e' ratio was also calculated as the ratio of the peak early diastolic mitral inflow per mitral annular early diastolic velocities. The test-retest mean errors between two observers for these LV functional indices were between 4% and 9%.

Conventional LV structural indices (interventricular septum and posterior wall thickness and LV internal dimensions) were assessed in parasternal M-mode. Left ventricular mass was estimated according to the Cube formula and was indexed for the body surface area (BSA) [120]. Relative wall thickness (RWT) was calculated as two times LV posterior wall thickness divided by the LV end-diastolic diameter.

The EchoPAC SWO by GE Ultrasound and the GcMat software package on MatLab (MathWorks, Inc., Natick, MA, USA) were used for the analyses [114].

3.2.2.4 Atrial Fibrillation (study IV)

The HUNT3 cohort was followed until November 30th, 2015. AF or atrial flutter diagnoses (ICD10 code I48) were retrieved from the hospital diagnoses register of the two regional hospitals. All medical records of those who had an AF diagnosis in the register were analysed, and ECGs were reviewed by experienced physicians. Only cases where the ECG showed evidence of AF or atrial flutter according to the standard criteria [49] were considered AF. In doubtful cases (n=17) a cardiologist and a specialist in internal medicine reviewed the medical record, and the case was discussed in a consensus meeting [121]. AF cases between 1988 and the baseline assessment were identified from the hospital records.

3.2.3 Covariates

3.2.3.1 *Socio-demographic variables*

In study I-III the highest achieved *education* was used as an indicator for socioeconomic status and was categorised as (i) primary or lower secondary school (≤ 9 years), (ii) upper secondary school (>9 and ≤ 12 years) and (iii) high school/university (>12 years). In study IV the Erikson Goldthorpe Parocarero occupational group scale was used [122]. The last reported occupation was transformed into an Erikson Goldthorpe Parocarero group, using the categories from a study in HUNT2 where original Erikson Goldthorpe Parocarero categories were related to common occupations in the Nord-Trøndelag County [122, 123]. The occupational categories were further categorized as: (i) higher grade professionals, such as legislators, managers, senior officers, medical doctors; (ii) lower grade professionals, such as technicians, managers of small businesses, secretaries; (iii) routine non-manual workers, such as clerks, service workers, shop assistants; and (iv) manual workers, such as agricultural workers, fishery workers, machine operators, and construction workers.

In study I and II *marital status* was categorized as (i) cohabiting and (ii) living alone. In study III and IV, the following categories were used: (i) never married, (ii) married or cohabiting and (iii) separated or widowed.

3.2.3.2 *Lifestyle factors*

Participants were classified as never, former and current smokers in study I-III and never, former, occasional and daily smoker in study IV. Smoking pack-years were also calculated in study I and II as the product of smoking duration (in years) and the average number of packets per day smoked during a year.

Participants reported the level and the average duration of their physical activity. The level of physical activity was considered intense if it caused sweating and heavy breathing or breathlessness. Otherwise, it was considered light activity. In study I and II, participants were categorized as: (i) inactive, if they reported less than one hour intense or less than three hours light physical activity; (ii) moderately active, in case of one to three hours intense or more than three hours light physical activity; and (iii) very active, in case of more than three hours intense physical activity per week. In study III, a physical activity index was available for the echocardiography cohort, which has been shown to have a good correlation with the VO₂ max value in a validation study [124]. In study IV, physical activity was categorized as: (i) physically inactive, in case of light to moderate physical activity at most 30-60 minutes per week, (ii) moderately active, in case of light to moderate physical activity more than 60 minutes a week and/or vigorous activity up to a maximum of 60 minutes a week and (iii) physically active, in case of vigorous activity more than 60 minutes a week.

3.2.3.3 Comorbidities

Participants were asked whether they have had any of the following chronic diseases: hypertension, angina pectoris, diabetes mellitus, cancer, asthma, goitre, hypothyroidism, hyperthyroidism, ankylosing spondylitis, rheumatoid arthritis, osteoporosis, epilepsy and fibromyalgia.

Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale which is a short screening instrument to self-assess anxiety and depression symptoms [125]. It was developed to screen for anxiety and depression in a clinical or primary care setting. The questionnaire encompasses seven questions with a four-point Likert-scale and contains subscales for anxiety and depression [125, 126].

3.2.3.4 Clinical measurements

Systolic and diastolic blood pressure was measured with Dinamap 845XT (Criticon/ GE Healthcare) on three consecutive occasions and the average of the second and third measurement was considered. Anthropometrics were measured with light clothes and without shoes: height and hip and waist circumference were rounded to the nearest centimetre and, weight was rounded to the nearest half kilogram. The waist circumference was taken horizontally through the umbilicus and the hip circumference was taken on the largest circumference of the hip. Body mass index (BMI) was calculated as weight (in kilograms) divided by the squared value of height (in meters).

Blood sample was taken in a non-fasting state and the time between the last meal and venipuncture [113] was recorded. Within two hours the blood serum was separated at the study centres and refrigerated at 4°C. The samples were analysed on the same day or if it was taken on Friday on the following Monday at the Central Laboratory of Levanger Hospital.[113] Serum concentration of total serum cholesterol, HDL cholesterol and triglycerides among other biomarkers were analysed [113].

3.3 STATISTICAL ANALYSES

3.3.1 Prospective analyses (studies I, II and IV)

3.3.1.1 Main analyses

The associations between alcohol consumption and the risk of AMI, HF and AF respectively were investigated using Cox proportional hazard models. The proportional hazard assumption was tested using formal tests of interaction with time, $\ln(\text{time})$ and with $\ln\text{-}\ln$ curves. We found no evidence against the proportionality assumption for the alcohol-related variables in any of the studies. If a covariate did not satisfy the proportionality assumption, we included it in the multivariate models as a time-dependent variable.

In all the three studies, the average amount of alcohol intake was modelled both as a categorical and as a continuous variable. To detect possible non-linear or threshold effects we tested the best fitting fractional polynomials in the multi-adjusted model in studies I and IV [127, 128] and modelled alcohol consumption with restricted cubic splines in study II [129].

In the base model, we adjusted for age and sex. In studies I and III, we further adjusted for education, marital status, smoking, physical activity and BMI. In study IV, we also included height and diabetes in the multi-adjusted model.

We further analysed whether adjustment for other possible confounders, such as waist-hip ratio, anxiety, depression, having diabetes (studies I and II) or high blood pressure influenced the strength of the observed associations. In study II, we also examined to what extent AMI during the follow-up mediates the association between alcohol consumption and the risk of HF. Therefore we excluded participants with a history of AMI before the baseline measurement and included AMI during the follow-up as a time-dependent variable.

To control for the sick-quitter bias, we studied the change in estimates after repeating our analyses after excluding abstainers who were former drinkers. In study I and II, we also examined the risk estimates in the different abstainer group categories. We compared the risk of AMI or HF for abstainers who were former drinkers, and drinkers with and without problem drinking to long-term abstainers.

We investigated whether the frequency of drinking was associated with the risk of AMI and HF with adjusting to the amount of alcohol consumption parallel with adjusting to drinking frequency. We examined whether the hazard ratios (HRs) differ among drinkers with and without problem drinking (studies I and II). In study IV, we further adjusted our multi-variable model for binge drinking and examined the change in the estimates. In study IV we also calculated the population attributable AF risk for alcohol consumption within the recommended limits (i.e., \leq seven drinks per week for women and \leq 14 drinks per day for men without risky drinking) using the %par macro in SAS [130].

We conducted beverage-specific analyses for beer, wine and spirits by examining the effect of one specific beverage while simultaneously adjusting for the other two types of alcoholic beverages.

3.3.1.2 Sensitivity analyses

In study I and II, we performed analyses when we included in the outcome only AMIs or HF's identified from hospital records; events that appeared only in the National Cause of Death Registry were excluded as they are more likely to have been misclassified. We also investigated separately fatal and non-fatal AMI in relation to alcohol consumption.

In all three studies, to decrease the possibility of reverse causation, we excluded events that occurred in the first five years of the follow-up. As participants with chronic diseases might

reduce their alcohol consumption, we examined the associations only among healthy participants without common chronic diseases.

We performed stratified analyses to examine potential effect modification by age, sex, smoking and BMI.

3.3.2 Cross-sectional analyses (study III)

We used general linear models to investigate the association between alcohol consumption and the echocardiographic functional and structural indices. Least square means of the functional indices (MAE, global longitudinal strain, global longitudinal strain rate, peak early diastolic and systolic mitral annular velocities (e' , S'), E/e' , E/A , TAPSE and RS') and of the structural indices (myocardial mass, wall thickness and dimensions) and 95% confidence intervals (CIs) were calculated across alcohol consumption categories. Apart from analysing the whole population, we also presented the sex-specific estimates in the main analyses as the reference values for most of the echocardiographic measurements are sex-specific [120, 131]. We also tested linear as well as quadratic trends. The multivariable model was adjusted for age, education, marital status, physical activity, smoking, BMI and sex (if not stratified). We further analysed whether including systolic blood pressure changes the estimates.

To test for the “sick quitters” bias [132], similarly to studies I-II and IV, we repeated our main analyses while excluding abstainers who reported alcohol intake during the previous HUNT. We examined whether adding drinking frequency to the multi-adjusted model modifies the observed associations between the quantity of alcohol consumption and LVF. To determine whether risky drinking modified the observed associations, we stratified our analyses by reported risky drinking.

We conducted stratified analyses by sex, age, (dichotomised at 50 years), smoking and BMI (dichotomised at 25 kg/m²) to address effect modification.

Statistical analyses were performed using SAS Enterprise Guide 6.0 (SAS Institute) and Stata IC/12.1 for Windows (Stata Corp LP).

4 RESULTS

4.1 QUANTITY OF ALCOHOL CONSUMPTION

4.1.1 Quantity of alcohol consumption and risk of AMI (study I)

There were 2 966 persons who had a first AMI during the 11.6 ± 2.5 years long follow-up (Figure2). The average alcohol consumption of those included in study I was 3.0 ± 4.8 g, and the majority of the study participants (41%) reported consumption of less than one alcoholic beverage over an average two week period (Table1). Drinkers were more likely to be male, younger, smokers and physically more active than abstainers or rare drinkers. The risk of AMI was lower among regular drinkers than among abstainers and rare drinkers, even after adjustment for several confounders (Table2).

Table2. HRs with 95% CIs for AMI according to the weekly amount of alcohol consumed

Groups according to average alcohol consumption	No. of events/ person-years	HR (95% CI)	
		Base model	Multi-adjusted model
Abstainers and rare drinkers*	1541 / 240 713	Reference	Reference
≥ 0.5 and ≤ 2.5 drinks per week	498 / 126 867	0.93 (0.84-1.04)	0.93 (0.85-1.06)
> 2.5 and ≤ 5 drinks per week	373 / 152 320	0.83 (0.74-0.94)	0.78 (0.68-0.89)
> 5 and ≤ 7 drinks per week	96 / 30 780	0.96 (0.78-1.19)	0.86 (0.71-1.01)
> 7 drinks per week	50 / 23 232	0.68 (0.51-0.91)	0.65 (0.48-0.87)

HR, hazard ratio; CI, confidence interval;

The base model was adjusted for age and sex (n = 58 827). The multi-adjusted model was adjusted for age, sex, level of education, marital status, level of physical activity, body mass index and problem drinking (n = 55 710).

*Consuming less than one drink in an average two week period.

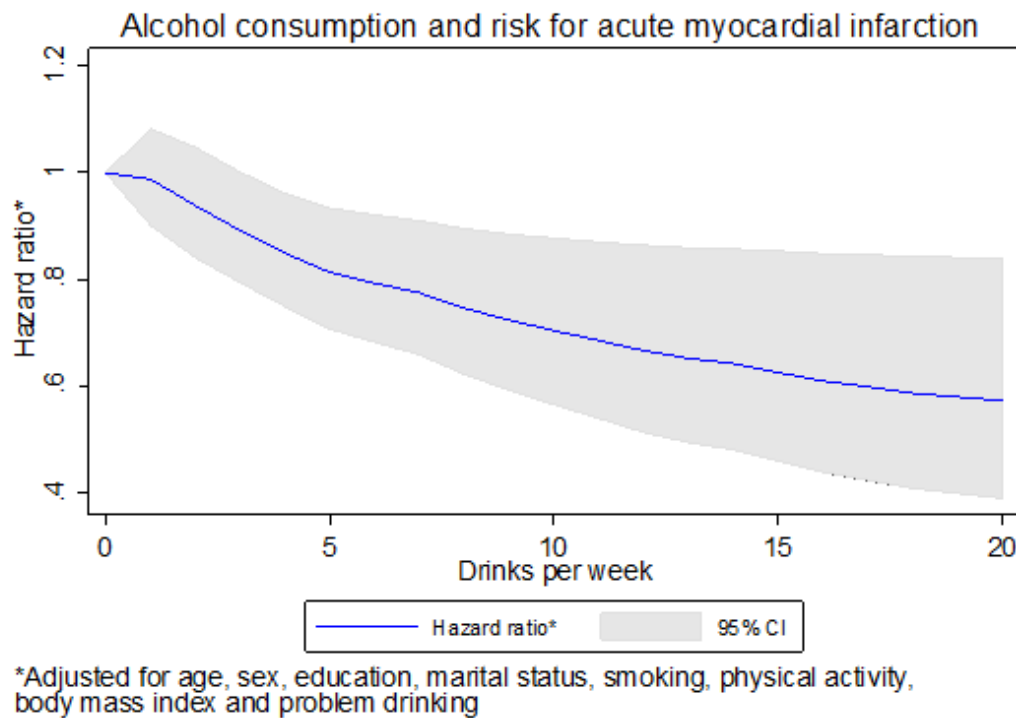
When we modelled alcohol consumption as a continuous variable, the best fitted fractional polynomial model showed a linear association between daily average alcohol intake and AMI risk. In the linear model, one drink increment of alcohol consumption was associated with a 28% lower AMI risk (adjusted HR 0.72, 95% CI 0.62–0.86) (Figure4). Additional adjustment for anxiety, depression, diabetes and blood pressure resulted in similar estimates. When we compared fatal and non-fatal AMI, the association was stronger in non-fatal AMI (multi-adjusted HR 0.67, 95% CI: 0.54-0.80) than for fatal AMI (multi-adjusted HR was 0.86, 95% CI: 0.64-1.15).

Table1. Baseline characteristics of the HUNT2 participants, free from history of AMI or HF at baseline, according to alcohol consumption (study I, II)

Study Variables	No. of participants		Alcohol consumption categories									
	Study I	Study II	<0.5 drinks week ⁻¹		≥0.5 and ≤2.5 drinks week ⁻¹		>2.5 and ≤5 drinks week ⁻¹		>5 and ≤7 drinks week ⁻¹		>7 drinks week ⁻¹	
	Study I	Study II	Study I	Study II	Study I	Study II	Study I	Study II	Study I	Study II	Study I	Study II
Categorical variables, %(n)												
Total	58 827	60 665	41(23 942)	41(25 043)	26(15 246)	26(15 619)	24(14 368)	24(14 661)	5(2 977)	5(3 028)	4(2 276)	4(2 314)
Sex(male)	46(27 086)	47(28 422)	33(7 996)	33(8 697)	43(6 614)	44(6 905)	58(8 338)	59(8 600)	74(2 214)	75(2 262)	85 (1 924)	85(1 958)
Smoking												
<i>Current</i>	29(16 910)	29(17 339)	23(5 385)	22(5 608)	29(4 453)	29(4 543)	34(4 928)	34(5 015)	40(1 179)	40(1 199)	42(965)	42(974)
<i>Former</i>	24(14 290)	25(15 214)	22(5 131)	23(5 619)	25(3 840)	26(4 048)	27(3 916)	28(4 091)	28(821)	28(849)	26(582)	26(606)
<i>Never</i>	47(27 581)	46(28 063)	56(13 387)	55(13 775)	46(6 965)	45(7 021)	38(5 523)	38(5 553)	33(977)	32(980)	32(729)	32(734)
Physical activity level												
<i>Inactive</i>	57(33 275)	70(34 449)	65(15 524)	65(16 299)	54(8 257)	54(8 465)	49(7 063)	49(7 210)	46(1 367)	46(1 396)	47(1 064)	47(1 079)
<i>Moderate</i>	34(20 208)	21(20 779)	29(7 037)	29(7 318)	37(5 570)	37(5 698)	39(5 631)	39(5 757)	39(1 145)	39(1 165)	36(825)	36(841)
<i>Very active</i>	9(5 344)	10(5 437)	6(1 381)	6(1 426)	9(1 437)	9(1 456)	12(1 674)	12(1 694)	16(465)	15(467)	17(387)	17(394)
Living alone	40(23 451)	40(24 018)	39(9 364)	39(9 800)	36(5 457)	36(5 531)	41(5 871)	41(5 943)	47(1 393)	47(1 405)	59(1 330)	58(1 339)
Education												
≤9 years	35(19 802)	36(20 843)	51(11 281)	52(11 975)	28(4 206)	29(4 392)	23(3 323)	24(3 462)	20(583)	20(597)	18(409)	18(417)
10-12 years	44(24 870)	44(25 325)	34(7 691)	34(7 888)	48 (7 232)	48(7 348)	51(7 181)	50(7 280)	53(1 546)	53(1 572)	54(1 220)	54(1 237)
>12 years	21(11 760)	21(11 915)	14(3 147)	14(3 206)	23 (3 502)	23(3 537)	26(3 679)	26(3 718)	28(809)	27(819)	28(623)	28(635)
Problemdr*	5.4(3 158)	5.3(3 211)	0.5(288)	0.5(295)	2.9(441)	2.9(456)	9.0(1 296)	9.0(1 313)	17.5(521)	17.4(528)	27(612)	27(619)
Continuous variables, mean (SD)												
Age	49.1(16.9)	49.7(17.1)	56.2(17.6)	56.9(17.6)	45.6(14.9)	46.1(15.1)	43.5(13.9)	43.9(14.1)	42.9(14.5)	43.2(14.6)	41.2(15.2)	41.6(15.4)
BMI	26.3(4.1)	26.3(4.1)	26.9(4.5)	26.9(4.5)	26.0(3.9)	26.0(3.9)	25.9(3.6)	25.9(3.6)	26.0(3.6)	26.0(3.6)	26.0(3.5)	26.1(3.5)
Anxiety	4.3(3.3)	4.2(3.3)	4.3(3.5)	4.2(3.5)	4.2(3.2)	4.2(3.2)	4.2(3.2)	4.2(3.2)	4.3(3.2)	4.3(3.2)	4.5(3.5)	4.5(3.5)
Depression	3.4(3.1)	3.5(3.1)	3.8(3.3)	3.9(3.3)	3.2(2.9)	3.2(2.9)	3.1(2.8)	3.1(2.8)	3.2(2.9)	3.2(2.9)	3.4(3.0)	3.4(3.0)
Systolic BP	137(22)	138(21)	142(24)	142(24)	133(20)	134(20)	133(18)	133(18)	135(18)	135(18)	136(17)	136(17)
Diastolic BP	81(12)	80(12)	81(13)	81(13)	79(12)	79(12)	79(12)	79(12)	80(12)	80(12)	80(12)	80(12)
HDL-C	1.39 (0.39)	1.38 (0.39)	1.37(0.38)	1.36(0.38)	1.40(0.39)	1.39(0.39)	1.39(0.39)	1.39(0.39)	1.38(0.39)	1.38(0.39)	1.38(0.39)	1.38(0.40)

BMI: body mass index; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; Blood pressure was measure in mmHg, and HDL-C in mmol/L. Anxiety and Depression was measured by the Hospital Anxiety and Depression Scale. *Problem drinkers, defined as at least two affirmatory answers in the CAGE questionnaire.

Figure 4. Multi-adjusted HRs with 95% CIs for AMI according to daily alcohol intake



4.1.2 Quantity of alcohol consumption and risk of HF (study II)

During the 11.2 ± 3.0 years long follow-up 1 588 first HF cases were identified, 1 134 from the hospital records and 454 exclusively from the cause of death register (Figure 2). Table 3 shows the multi-adjusted HRs for HF according to alcohol consumption categories. The risk of HF was lower among drinkers compared to non-drinkers (Table 3).

Table 3. HRs with 95% CIs for HF according to the weekly amount of alcohol consumed

Groups according to average alcohol consumption	No. of events/ person-years	HR (95% CI)	
		Base model	Multi-adjusted model
Abstainers and rare drinkers*	1158/ 270 942	Reference	Reference
≥ 0.5 and ≤ 2.5 drinks per week	235 /181 250	0.88 (0.77-0.99)	0.85 (0.73-0.99)
> 2.5 and ≤ 5 drinks per week	138 / 169 067	0.76 (0.63-0.91)	0.72 (0.60-0.88)
> 5 and ≤ 7 drinks per week	34 / 34 237	0.87 (0.62-1.23)	0.89 (0.62-1.27)
> 7 drinks per week	23 / 25 636	0.80 (0.53-1.24)	0.82 (0.54-1.25)

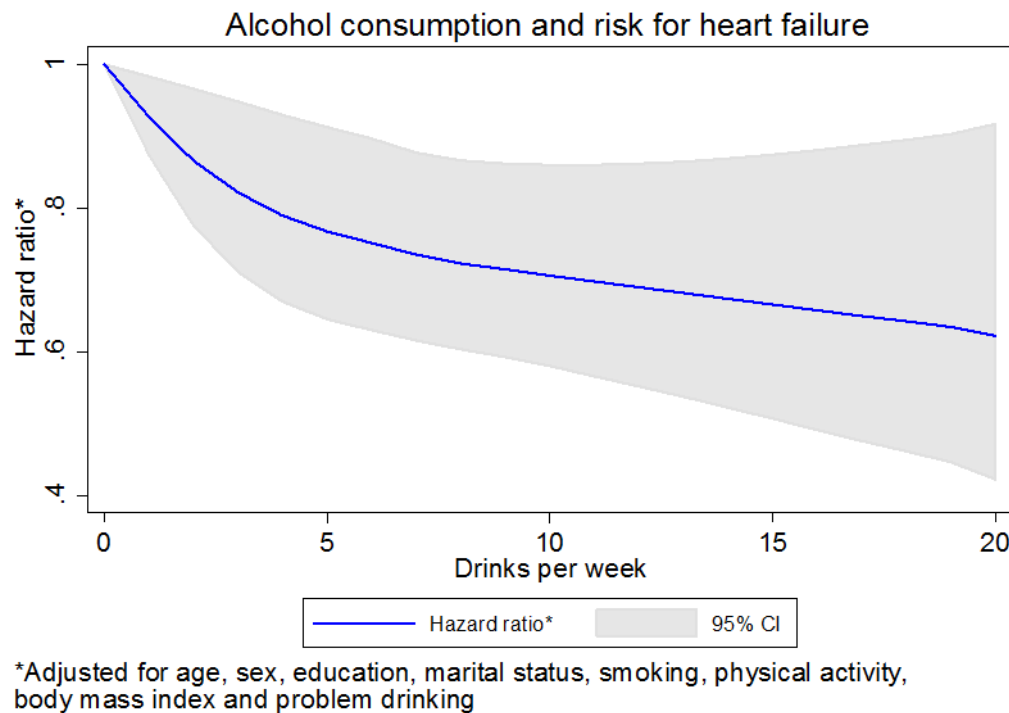
HR, hazard ratio; CI, confidence interval;

The base model was adjusted for age and sex (n = 60, 665). The multi-adjusted model was adjusted for age, sex, level of education, marital status, level of physical activity, body mass index and problem drinking (n = 57 318).

*Consuming less than one drink in an average two week period.

Adding waist-hip ratio, anxiety or depression to the multi-adjusted model did not alter the association between alcohol consumption and HF substantially. The continuous model showed a non-linear association ($p < 0.001$) (Figure 5).

Figure 5 Multi-adjusted HRs with 95% CIs for HF according to daily alcohol consumption



4.1.3 Quantity of alcohol consumption and LV function (study III)

The majority of the study participants in study III were light drinkers, consuming less than three drinks per week; only 4.5% of the participants reported more than seven alcoholic drinks per week (Table 4). Table 5 shows the association between the quantity of alcohol intake and LV indices, which were largely similar across the different alcohol intake categories. LV mass and LV end diastolic dimension were positively associated with alcohol consumption (Table 6).

Table 4. Baseline characteristics of the study participants according to alcohol consumption (study III)

Study variables	No. of participants		Alcohol consumption categories							
	Women	Men	<0.5 drinker week ^{-1*}		≥0.5 and ≤3 drinker week ⁻¹		>3 and ≤7 drinker week ⁻¹		>7 drinker week ⁻¹	
			Women	Men	Women	Men	Women	Men	Women	Men
Total	613	566	98	86	364	344	123	110	28	26
Categorical variables, n(%)										
Education										
<i>Primary-Secondary</i>	86(400)	67(376)	64(61)	75(63)	66(244)	68(234)	67(81)	61(66)	50(14)	50(13)
<i>Tertiary</i>	24(205)	33(187)	36(34)	26(22)	33(117)	32(109)	33(40)	40(43)	50(14)	50(13)
Smoking										
<i>Never-former</i>	77 (451)	74 (435)	83 (46)	76 (70)	74 (451)	78 (266)	70 (86)	75 (83)	64 (18)	62 (16)
<i>Current</i>	23 (153)	26 (126)	17 (23)	24 (14)	26 (84)	22 (75)	30 (36)	25 (27)	36 (10)	38 (10)
Marital status										
<i>Living alone</i>	41 (249)	36 (203)	47 (46)	36 (47)	39 (142)	33 (115)	40 (49)	39 (43)	43 (13)	54 (14)
<i>Cohabiting, married</i>	59 (363)	64 (362)	53 (52)	64 (55)	61 (222)	67 (228)	60 (73)	61 (67)	57 (16)	46 (12)
Continuous variables, mean (SD)										
Age (years)	49.3(13.6)	49.0(13.5)	49.1(14.9)	51.4(15.5)	49.2(13.7)	49.0(13.0)	49.6(13.2)	48.4(13.1)	49.6(11.7)	44.0(12.7)
Body mass index (kg/m ²)	26.3 (4.0)	26.3 (3.7)	27.3 (4.9)	27.3 (4.6)	26.1 (3.9)	26.1 (3.7)	26.2 (3.7)	26.2 (3.3)	25.9 (2.4)	25.9 (2.9)
Physical activity index	2.1 (0.8)	2.2 (0.8)	2.0 (0.8)	2.1 (0.7)	2.2 (0.8)	2.1 (0.8)	2.0 (0.9)	2.2 (0.8)	2.1 (0.8)	2.2 (0.8)
Systolic blood pressure	127 (17)	133 (14)	127 (17)	132 (15)	127 (17)	133 (14)	126 (16)	133(14)	130 (25)	133 (12)
Diastolic blood pressure	71 (10)	77 (10)	70 (9.6)	77 (10)	71 (10)	77 (10)	73 (10)	77 (10)	75 (13)	74 (8)

*Reported consuming less than one alcoholic drink consumption in a regular two week period. Blood pressure was measured in Hgmm

Table 5. Least square means and 95% CIs for LV functional indices according to the weekly amount of alcohol consumed

	N	Least square means* (95% CI) of alcohol consumption categories				P-values	
		Non-drinkers	≥0.5 and ≤3 drinks week ⁻¹	>3 and ≤7drinks week ⁻¹	>7 drinks week ⁻¹	Linear	Quadratic
Mitral Annular Excursion (cm)							
Men	534	1.57 (1.51, 1.63)	1.57 (1.54, 1.61)	1.59 (1.54, 1.64)	1.64 (1.55, 1.74)	0.18	0.37
Women	544	1.57 (1.52, 1.63)	1.59 (1.56, 1.63)	1.61 (1.56, 1.66)	1.57 (1.47, 1.67)	0.98	0.34
Global longitudinal strain (%)							
Men	548	-15.9 (-16.4,-15.3)	-16.0 (-16.2,-15.7)	-16.0 (-16.2,-15.5)	-16.2 (-17.1,-15.2)	0.70	0.59
Women	587	-17.7 (-18.2,-17.3)	-17.4 (-17.6,-17.1)	-17.3 (-17.7,-16.8)	-17.1 (-17.9,-16.2)	0.34	0.42
Global longitudinal strain rate (s⁻¹)							
Men	513	-1.01 (-1.04,-0.98)	-1.04 (-1.06,-1.03)	-1.04 (-1.07,-1.02)	-1.00 (-1.06,-0.95)	0.74	0.05
Women	548	-1.02 (-1.05,-0.99)	-1.02 (-1.03,-1.00)	-1.04 (-1.06,-1.01)	-1.04 (-1.09,0.99)	0.34	0.89
Peak early diastolic mitral annular velocity (e') (cm/s)							
Men	528	11.1 (10.4, 11.7)	10.6 (10.3, 10.9)	11.1 (10.6, 11.7)	11.6 (10.4, 12.9)	0.40	0.44
Women	556	11.6 (11.0, 12.2)	11.6 (11.3, 11.9)	12.2 (11.6, 12.7)	11.5 (11.4, 13.5)	0.10	0.67
Peak systolic mitral annular velocity (S') (cm/s)							
Men	520	8.72 (8.38, 9.05)	8.63 (8.44, 8.83)	8.83 (8.54, 9.11)	9.07 (8.51, 9.63)	0.30	0.87
Women	556	8.13 (7.86, 8.40)	8.27 (8.10, 8.43)	8.20 (7.95, 8.45)	8.20 (7.71, 8.69)	0.69	0.85
E/A ratio							
Men	552	1.41 (1.29, 1.53)	1.38 (1.31, 1.45)	1.42 (1.32, 1.53)	1.31 (1.11, 1.50)	0.48	0.49
Women	586	1.37 (1.28, 1.46)	1.36 (1.30, 1.41)	1.34 (1.36, 1.42)	1.31 (1.14, 1.47)	0.41	0.90
E/e' ratio							
Men	545	6.92 (6.24, 7.59)	7.24 (6.86, 7.63)	6.83 (6.26, 7.40)	6.81 (5.71, 7.92)	0.74	0.60
Women	580	6.52 (5.96, 7.01)	6.67 (6.33, 7.00)	6.27 (5.76, 6.79)	6.34 (5.33, 7.34)	0.61	0.99
Peak tricuspid annular systolic velocity (RS') (cm/s)							
Men	549	12.9 (11.9, 12.7)	12.8 (12.3, 12.8)	13.0 (12.2, 13.0)	13.0 (11.8, 13.2)	0.76	0.91
Women	587	12.3 (12.4, 13.4)	12.5 (12.5, 13.0)	12.6 (12.6, 13.4)	12.5 (12.1, 13.8)	0.57	0.39
Tricuspid annular plane systolic excursion (TAPSE) (cm)							
Men	570	2.80 (2.66, 2.94)	2.85 (2.78, 2.92)	2.94 (2.82, 3.06)	2.84 (2.61, 3.08)	0.91	0.31
Women	527	2.72 (2.62, 2.83)	2.81 (2.75, 2.87)	2.78 (2.69, 2.88)	2.74 (2.55, 2.93)	0.59	0.33

*Means are adjusted for age, marital status and education, smoking, physical activity and body mass index.

Table 6. Least square means and 95% CIs for LV structural indices according to the weekly amount of alcohol consumed

	N	Least square means* (95% CI) of alcohol consumption categories (drinks per week)				P-values	
		Non-drinkers	≥0.5 and ≤3 drinks week ⁻¹	>3 and ≤7drinks week ⁻¹	>7 drinks week ⁻¹	Linear	Quadratic
LV mass (gr)							
Men	551	157.0 (146.8 - 167.2)	158.6 (153.1 - 164.0)	169.5 (160.7 - 178.2)	182.1 (164.6 - 199.7)	<0.01	0.92
Women	578	151.6 (142.0 - 161.2)	159.5 (154.1 - 164.9)	169.3 (160.6 - 177.9)	180.0 (162.7 - 197.3)	<0.01	0.13
LV mass per body surface area (gr/m²)							
Men	550	76.8 (71.5 - 82.1)	78.6 (75.8 - 81.4)	83.0 (78.5 - 87.5)	91.4 (82.3 - 100.4)	<0.01	0.67
Women	577	86.1 (80.4 - 91.8)	90.4 (87.2 - 93.6)	95.5 (90.4 - 100.6)	102.6 (92.4 - 112.8)	<0.01	0.02
LV end diastolic diameter (mm)							
Men	548	50.7 (49.5 - 51.9)	50.9 (50.3 - 51.5)	51.0 (50.0 - 52.0)	52.1 (50.0 - 54.2)	0.03	0.23
Women	577	49.4 (48.3 - 50.5)	50.4 (49.8 - 51.1)	51.4 (50.4 - 52.4)	52.5 (50.5 - 54.6)	0.07	0.31
LV end systolic diameter (mm)							
Men	548	32.3 (31.2 - 33.4)	32.4 (31.8 - 33.0)	32.4 (31.5 - 33.4)	33.9 (31.9 - 35.8)	0.17	0.29
Women	577	31.1 (30.1 - 32.1)	32.2(31.6 - 32.8)	32.7 (31.8 - 33.7)	34.6 (32.8 - 36.5)	<0.01	0.48
Relative wall thickness (cm)							
Men	551	0.25 (0.24 - 0.26)	0.26 (0.25 - 0.26)	0.27 (0.27 - 0.27)	0.27 (0.25 - 0.28)	0.07	0.96
Women	578	0.26 (0.25 - 0.27)	0.26 (0.26 - 0.27)	0.26 (0.26 - 0.27)	0.27 (0.26 - 0.28)	0.47	0.31

*Adjusted for age, marital status, education, smoking, physical activity and body mass index

4.1.4 Quantity of alcohol consumption and risk of AF (study IV)

Overall, 23% of participants included in Study IV reported intake of more than three drinks per week and the average alcohol consumption in the population was 3.8 ± 4.8 g (Table 7).

Alcohol consumption was associated with an increased risk of AF over seven drinks per week intake when compared to non-drinkers (Table 8). The risk of AF was similar among non-drinkers, rare drinkers and light drinkers. Further adjustment for waist-hip ratio, anxiety, depression, or blood pressure did not change the estimates considerably. We also modelled alcohol consumption as a continuous variable in a linear model, where the HR for a one-drink increment was 1.03 [95% CI: 1.01-1.04]. The best fitting fractional polynomial indicated a curvilinear association instead of a truly linear one (Figure 6).

Table7: Baseline characteristics of the HUNT3 participants, free from a history of AF at baseline, according to alcohol consumption (study IV)

Study variables	No. of participants	Alcohol intake categories (drinks week ⁻¹)				
		Abstainers	Rare-drinkers*	>0 and ≤3	>3 and ≤7	>7 drinks week ⁻¹
Total	47 002	5 302	6 212	24 792	8 391	2 305
Categorical variables, % (n)						
Sex (female)	55 (25 885)	70 (3 719)	69 (4 271)	57 (14 216)	37 (3 143)	23 (536)
Physical activity						
Inactive	22 (10 100)	26 (1 327)	25 (1 525)	20 (4 959)	21 (1 727)	24 (562)
Moderate	42 (19 562)	52 (2 624)	45 (2 784)	42 (10 282)	37 (3 098)	34 (774)
Active	36 (16 808)	22 (1 083)	30 (1 832)	38 (9 389)	42 (3 545)	42 (959)
Smoking						
Current	25 (11 415)	16 (830)	22 (1 383)	24 (5 902)	30 (2 512)	35 (788)
Former	34 (14 850)	25 (1 273)	28 (1 707)	33 (7 983)	36 (3 012)	38 (875)
Never	42 (19 910)	59 (2 986)	49 (2 993)	43 (10 534)	33 (2 780)	27 (617)
Living in a relationship	24 (11 128)	17 (891)	26 (1 616)	23 (5 639)	26 (2 188)	35 (794)
Binge drinker**	3 (1 552)	0 (0)	0 (0)	1 (152)	7 (582)	35 (818)
Problem drinker‡	9 (3 001)	3 (40)	3 (101)	5 (1 035)	17 (1 157)	39 (668)
Previous CVD†	9 (4 414)	17 (925)	11 (691)	8 (2 039)	7 (582)	8 (177)
Chronic disease#	69 (24 929)	59 (3 692)	59 (3 678)	50 (12 518)	47 (3 947)	48 (1 094)
Continuous variables, mean (SD)						
Age, years (n=47,002)	52.3 (15.7)	62.3(16.8)	53.5(17.2)	51.2 (14.6)	49.5 (14.0)	47.6 (15.5)
BMI, kg/m ² (n=46,683)	27.1 (4.4)	27.7 (4.9)	27.7 (5.0)	27.0 (4.3)	26.9 (3.9)	26.8 (3.9)
HDL-C (n=45,677)	1.3 (0.35)	1.3 (0.3)	1.3 (0.3)	1.4 (0.3)	1.4 (0.4)	1.3 (0.4)
Systolic BP (n=46,739)	130 (19)	135 (21)	130 (20)	129 (18)	131 (17)	133 (17)
Diastolic BP (n=46,739)	73 (11)	73 (12)	72 (11)	73 (11)	75 (11)	75 (12)
Anxiety (n=36,563)	4.01 (3.3)	4.2 (3.7)	4.2 (3.6)	4.0 (3.2)	3.9 (3.2)	4.0 (3.3)
Depression (n=36,777)	3.3 (2.9)	3.9 (3.2)	3.6 (3.1)	3.1 (2.8)	3.0 (2.7)	3.3 (2.9)

SD: standard deviation; CVD: cardiovascular diseases; BMI: body mass index; HDL-C: high density lipoprotein cholesterol, measured in mmolL⁻¹; BP: blood pressure, measured in Hgmm

*Defined as reporting consuming alcohol during the last year, but not during the past two weeks.

**Binge drinkers were defined as drinking ≥ 5 drinks in one setting at least once a week.

‡Defined as has at least two affirmative answers in the CAGE questionnaire.

†Defined as ever having acute myocardial infarction, angina pectoris, heart failure, other heart disease and/or stroke/brain haemorrhage.

#Defined as ever having any of the following: hypertension, diabetes, angina pectoris, heart failure, other heart disease, stroke/brain haemorrhage, kidney disease, asthma, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, cancer, epilepsy, rheumatoid arthritis, Bechterev's disease, sarcoidosis or osteoarthritis.

Table 8. HRs with 95% CIs for AF according to the weekly amount of alcohol consumed

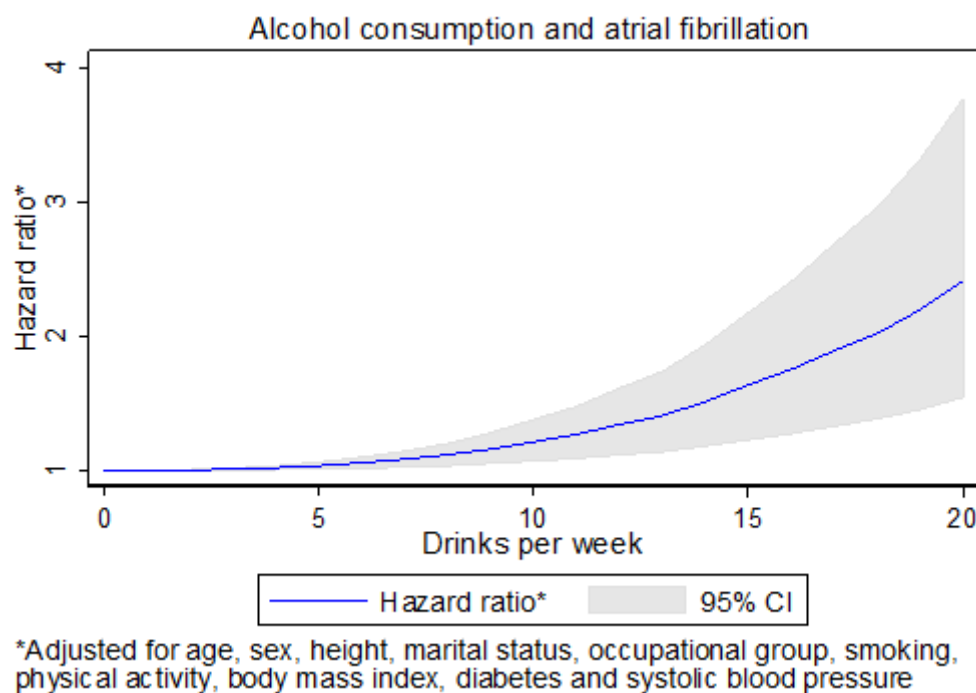
Groups according to average alcohol consumption	No. of events/ Person years	HR (95% CI) Base model	Multi-adjusted model*
Abstainers	347/ 41,694	Reference	Reference
Rare-drinkers†	258/ 50,411	1.03 (0.88-1.21)	1.04 (0.88-1.24)
>0 and ≤3 drinks per week	725/ 205,234	0.94 (0.82-1.08)	1.00 (0.87-1.63)
>3 and ≤7 drinks per week	225/ 68,994	1.00 (0.83-1.19)	1.05 (0.87-1.28)
>7 drinks per week	77/ 18,434	1.25 (0.97-1.62)	1.38 (1.06-1.80)

HR: hazard ratio; CI: confidence interval.

*The base model was adjusted for age and sex (n= 47 002). The multi-adjusted model was adjusted for age, sex, height, body-mass index, marital status, socio-economic position, exercise, smoking, binge drinking and diabetes (n=45 193).

† Rare drinkers were defined as those who reported alcohol consumption during the last year, but not during the last two weeks.

Figure 6. Multi-adjusted HRs with 95% CIs for AF according to weekly alcohol consumption



The cut-point where the risk deviated from the null occurred at around four-five drinks per week consumption. The predicted HR at an intake of four drinks per week was 1.02 (95% CI: 1.01-1.03) and 1.08 (95% CI: 1.03-1.15) for seven drinks increment. The AF incidence attributable to alcohol consumption was 1.6% (95% CI: 0.6%-2.7%) when any drinkers were compared to non-drinkers.

4.2 THE EFFECT OF FORMER DRINKING

The majority of abstainers in HUNT2 had information on their alcohol consumption in HUNT1 (Figure 2). When we compared the risk of AMI and HF of abstainers who were previous drinkers with that of long-term abstainers (n=341 in study I and n=373 in study II), we found that former drinkers had a slightly higher risk of both AMI (adjusted HR was 1.29, 95% CI: 0.75-1.70) and HF (multi-adjusted HR was 1.33, 95% CI: 0.87-2.12). However, when we excluded abstainers who were former drinkers from the analyses the estimates remained mostly the same.

In study III and IV, we used information on previous alcohol consumption from the HUNT2 (Figure 3). Excluding abstainers who were former drinkers (n=117 in study III and n=447 in study IV) did not influence the association of alcohol consumption with LV function or with risk of AF.

4.3 THE ROLE OF PROBLEM DRINKING (STUDIES I-II) AND RISKY DRINKING (STUDIES III-IV)

In study I and II, we compared the risk of AMI and HF between drinkers regarding problem drinking (had at least two affirmative answers on the CAGE questionnaire). We found that problem drinkers had a similar risk of AMI as drinkers without problem drinking. The multi-adjusted HR for AMI in drinkers without problem drinking was 0.79 (95% CI: 0.69-0.90), and for drinkers with problem drinking was 0.81 (95% CI: 0.62-1.06) when compared to long-term abstainers. However, the risk of HF tended to be higher among drinkers with problem drinking (multi-adjusted HR: 1.27, 95% CI: 0.38-4.26) than drinkers without problem drinking (multi-adjusted HR was 0.80, 95% CI: 0.68-0.95) when compared to long-term abstainers as the reference group.

In Study III, we stratified our analyses by risky and non-risky drinkers and found that the means of the LV functional indices in different alcohol consumption categories did not differ between risky and non-risky drinkers. Similarly, there was no association between the amount of alcohol intake and LV functional indices in any of the groups. The positive association between alcohol intake and LV mass indices was stronger among risky than among non-risky drinkers. The multi-adjusted mean of the body surface area indexed LV mass for those who reported more than three but at most seven drinks per week was 82 g (95% CI: 77-88 g) among non-risky drinkers and 93 g (95% CI: 89-98 g) among risky drinkers, respectively.

In study IV, adjusting for binge drinking did not change the estimates essentially. However, the attributable proportion for alcohol consumption within the recommended limits (i.e. ≤ 7 drinks per week for women and ≤ 14 drinks per week for men, and in the absence of risky drinking), when compared to non-drinkers was only 0.07% (95% CI: -0.01%, 0.13%).

4.4 FREQUENCY OF DRINKING (STUDIES I-IV)

We found that higher drinking frequency was associated with a lower risk of AMI and HF, respectively independently of the quantity of alcohol intake. The adjusted HRs for AMI were 0.93 (95% CI 0.83-1.04) for intakes of one to four, 0.78 (95% CI 0.63-0.97) for five to 12, and 0.76 (95% CI 0.50-1.16) for more than 12 times per month. For HF risk the HRs was 0.98 (95%: 0.56-1.11) for those who reported drinking one to four and 0.79 (95% CI: 0.83-1.16) for those who reported alcohol intake five times or more when compared to those who reported drinking less than once in a month. The estimates did not differ according to drinking frequency in study III and IV.

4.5 BEVERAGE SPECIFIC ANALYSES (STUDIES I-IV)

When we investigated the effect of the different beverages types, we found similar estimates. However, beer consumption was associated with a slightly lower risk of AMI than wine or spirit consumption. The adjusted HRs were 0.76 (95% CI: 0.63-0.91) for beer and 0.68 (95% CI: 0.56-0.82) for wine and for spirit consumption.

4.6 MEDIATION BY AMI (STUDY II)

A total of 1 712 AMI cases were detected before the follow-up and 3 171 during the follow-up in study II. Among those who had HF during the follow-up, 349 participants had AMI before the baseline and 133 AMI cases occurred during the follow-up period. When we excluded participants with a history of AMI before the baseline and adjusted for AMI during the follow-up as a time-dependent variable in our multi-adjusted model, we observed a slight change of the estimate. The multi-adjusted HR comparing participants drinking more than two drinks to those who reported alcohol consumption up to two drinks per week increased to 0.84 (95% CI: 0.65-1.09) from 0.79 (95% CI: 0.62-0.98).

4.7 EFFECT MODIFICATION AND SENSITIVITY ANALYSES (STUDIES I, II AND IV)

We did not find evidence for effect modification by age, sex, exercise, smoking BMI or high blood pressure in any of the studies.

When we restricted our analyses to events diagnosed in hospitals (n=1 947 AMI cases and n=1 134 HF cases) the strength of the association remained the same for AMI (the multi-adjusted HR was 0.74, 95% CI: 0.62-0.88) and there was a slight reduction in the relative risk for HF (multi-adjusted HRs 0.85, 95% CI: 0.67-1.11).

Excluding participants with any of the following chronic conditions; as hypertension, stroke, angina pectoris, diabetes mellitus, cancer, asthma, goitre, hypothyroidism, hyperthyroidism, ankylosing spondylitis, rheumatoid arthritis, osteoarthritis, epilepsy or fibromyalgia from the analyses did not considerably influence the association between alcohol consumption and risk of AMI, HF or AF.

The exclusion of the first five years of the follow-up did not weaken the associations between alcohol intake and AMI and HF. For AF, the risk estimate was slightly lower after excluding the first four years of the follow up. The adjusted HR, – when comparing participants who reported consuming more than seven drinks per week to participants who reported up to this amount, – was 1.28 (95% CI: 1.05-1.53).

5 DISCUSSION

5.1 SUMMARY OF MAIN FINDINGS

Light to moderate alcohol intake was associated with a lower risk of AMI and HF, and slightly increased risk of AF over seven drinks per week of average alcohol intake. We found no evidence for an association between LV function and light to moderate alcohol consumption. The associations did not change substantially after excluding abstainers, who reported consuming alcohol in the previous phases of the HUNT study, and it persisted also after extensive adjustments for sociodemographic, psychosocial and lifestyle factors and the presence of common chronic disorders. Frequent, low level of alcohol consumption was associated with a lower AMI and HF risk than less frequent intake. Furthermore, drinking within the recommended limit, i.e. up to seven drinks per week for women and up to 14 drinks per week for men without binge and/or problem drinking was not associated with an increased risk of AF. Drinkers with problem drinking had a lower risk of AMI, but slightly higher risk of HF than abstainers. However, the statistical power to investigate the latter association was very limited. Among risky drinkers, even if the average alcohol intake remained within the recommended levels the quantity of alcohol consumption was positively associated with LV mass indices.

5.2 COMPARISON WITH PREVIOUS STUDIES

5.2.1 Quantity of alcohol consumption and risk of AMI, HF and AF

5.2.1.1 *Acute myocardial infarction (study I)*

Our finding, that alcohol consumption was inversely associated with the risk of AMI, is in line with the majority of the previous studies in this field [24, 26]. In this low drinking population, where the average alcohol consumption was only 3.0 ± 4.8 g per day, we observed a linear reduction of AMI risk with increasing alcohol intake. However, we could not draw inference on higher alcohol intake categories as excessive consumption was limited in this population. Only 2.8% of the study participants reported an alcohol intake of more than seven drinks per week. The most up-to-date meta-analysis showed maximal protection was afforded against IHD when consuming one to two drinks per day of average alcohol intake among women and one to four drinks per day of average alcohol intake among men when compared to abstainers [24, 26, 29]. Excluding abstainers, who were former drinkers in our study, had no considerable effect on the estimates, suggesting that the association was not driven by sick-quitters. This corroborates the findings of the earlier studies that could either separate abstainers who were former drinkers from long-term abstainers [24, 105] or investigated this question in a young adult population [133].

5.2.1.2 *Heart failure and left ventricular function (study II, III)*

A recently published meta-analysis [15], which has already incorporated the results of our study II, concluded that relative to abstainers light alcohol consumption (up to 7 drinks per

week) was associated with an approximately 14% lower risk of HF. Moderate drinkers (7-14 drinks per week) had on average a 10% lower risk of HF. Some studies, including our, could separate abstainers who were former drinkers from long-term abstainers, and their meta-analyses showed that abstainers who were former drinkers had a higher HF risk than long-term abstainers. Furthermore, we confirmed that the inverse association between alcohol intake and HF persisted even when former drinkers were excluded.

In study III, we examined the association between light to moderate alcohol consumption and LV function among healthy individuals, but we found no clear evidence that light to moderate alcohol intake would be associated with a better LV function. In a recent population-based study [58], decreased left ventricular ejection fraction was inversely associated with alcohol intake. The lowest risk for modest ejection fraction impairment was found among those who consumed at most one alcoholic drink per day. Another study, which was conducted in an elderly population and used sensitive echocardiography similar to that used in our study, did not find any clear association between light to moderate alcohol consumption and LV function [64]. While the authors described an inverse, but clinically irrelevant association between alcohol intake and LV ejection fraction among women, they found no association between moderate alcohol intake and LV functional characteristics among men. Lastly, a Chinese study in a middle-aged population demonstrated a worse LV function among those who consumed over six drinks per week than among non-drinkers [134]. However, it should be mentioned that many individuals with an East Asian origin have a slower metabolism than individuals with a Caucasian origin. This results in a longer stay of acetaldehyde, the cardiotoxic metabolite of alcohol, in the bloodstream [135, 136]. It may explain the discrepancy in results between our and other studies conducted in mainly Caucasian populations and the Chinese-study [64].

5.2.1.3 Atrial fibrillation (study IV)

The majority of the previous studies reported an association between alcohol intake and increased AF risk, with an approximately 8% risk increase for a one drink increment [7, 26, 31, 32, 69, 70, 137]. We also found an increased risk of AF with increasing alcohol consumption, with around a 3% risk increase for a one drink increment in the linear model. However, our categorical analyses suggested that the risk increase became important only above seven alcoholic drinks per week. When alcohol consumption was modelled as a continuous variable with fractional polynomials, the risk function showed a somewhat curvilinear shape with the first slight increase around 4 to 5 drinks per week and a steep increase over 14 alcoholic drinks. The previous meta-analyses in this field could not conclude whether the risk increase is truly linear [7, 70] or it is more threshold like [31]. Our results support the later, i.e. that AF risk may not increase considerably up to seven alcoholic drinks per week. Excluding former drinkers did not influence the association.

5.2.2 Drinking frequency, binge- and problem drinking and risk of AMI, HF and AF

There is increasing evidence suggesting that more frequent alcohol intake within the same amount of consumption may be associated with more favourable health outcomes [10, 28, 29, 74, 81, 138]. Our findings corroborate those of previous studies showing that those who frequently consume alcohol have the lowest risk of AMI, while occasional heavy alcohol intake is associated with the least favourable AMI risk even within moderate consumption [10, 28, 29]. Binge drinking has earlier been shown to eliminate the protective association between alcohol consumption and CVD [28, 29, 139-141]. Binge drinking may trigger AMI through an acute increase in sympathetic and thrombotic activity [28, 29, 75, 76, 142]. Though we had no direct information on binge drinking in studies I and II, problem drinking was measured by the CAGE questionnaire. Those who gave two affirmative answers on the questionnaire were more likely to have unhealthy drinking habits and, to be regular binge drinkers than those with no or one positive answer on CAGE [118]. In study I, we did not find considerable differences in AMI risk between drinkers with and without problem drinking behaviour. In contrast, in study II, alcohol intake was not associated with a lower risk of HF among drinkers with problem drinking compared to abstainers. This finding is in line with studies that found an increased risk of HF among binge drinkers compared to abstainers [14-16]. Furthermore, within the same amount of alcohol intake, more frequent drinking was associated with a lower risk of HF, than less frequent drinking. Our results seem to support that a pattern similar to that observed for IHD also exists for HF. Frequent low-level alcohol consumption seems to have the most favourable association both with AMI and HF [74].

As binge drinking was assessed explicitly in HUNT3, we could examine the effect of binge and/or problem drinking in studies III and IV. In study III, we found that among risky drinkers the quantity of alcohol consumption was associated with worsening values of LV structural indices. No similar association was found among individuals without risky drinking. We observed a very slight, but clinically irrelevant trend toward a better LV function in the latter group. Experimental studies suggest that binge drinking may trigger an inflammatory response in the myocytes, and may increase the susceptibility to ischemic injury [79]. Binge drinking may also induce myocardial oxidative stress and may decrease the activity of the mitochondrial complex in the myocardium [59]. In animal models, this was shown to lead to macro- and microvascular dysfunction [143] and to a remodelling of the myocardium [14, 16, 144, 145]. There is compelling evidence suggesting that binge drinking increase the risk of supraventricular arrhythmias [32, 65, 66, 77, 146-148]. To our knowledge, only one previous study examined the association between binge drinking and AF risk among light to moderate drinkers [149]. This study, conducted among cardiac patients found that binge drinkers who were otherwise moderate drinkers (drinking up to 21 drinks per week) have similarly high risk of AF as those, who consume more than 21 drinks per week [149]. In Study IV, when we excluded individuals who consumed alcohol over the recommended limits, i.e., >seven drinks per week for women and >14 drinks per week for

men or who reported binge or problem drinking [82] we did not find an increased risk of AF. Studies examining the effects of acute alcohol infusion showed that alcohol bingeing may lead to cardiac arrhythmias through alteration in the electrophysiological properties of the myocytes by modifying ion-channel functions [32, 66, 146, 148]. Binge drinking stimulates the sympathetic nervous system and inhibits vagal activity, which also facilitates arrhythmogenic activities [32, 66, 146, 148].

5.2.3 The effect of beverage types

We did not find clear support for the hypothesis that the association of alcohol intake and the risk of HF and AF or with LV function differs by the type of alcoholic beverage. The inverse association between the quantity of alcohol intake and AMI risk was slightly weaker for beer consumption than for wine and spirit consumption. Though findings from earlier studies concerning differences in CVD risk according to the type of alcoholic beverages have not been fully consistent, it seems that ethanol is the active substance that may primarily be responsible for the anti-atherosclerotic effect [10, 13, 25, 74, 86]. Polyphenols, which are primarily found in wine, may have some additional health benefits, due to their antioxidant properties [88, 91, 94, 100]. Our finding that wine and spirits were similarly associated with AMI and HF risk is supportive of the hypothesis that alcohol is the active substance. The weaker association between beer and AMI risk than that observed in the case of the two other types of beverage may be due to its lowest alcohol content.

5.2.4 The role of AMI in the association between alcohol consumption and HF risk

A substantial proportion of HF cases have an ischemic aetiology [44] and HF is a common complication after AMI [44, 61]. More than one-third of AMI patients will eventually develop HF [44, 150]. As moderate alcohol consumption may slow down the atherosclerotic processes, the observed protective effect of light to moderate alcohol intake on HF risk may be mediated through IHD. Some studies conducted among AMI patients could not find an inverse association between light-moderate alcohol intake and HF risk [63, 151]. Other studies found that light to moderate alcohol intake was associated with a reduced HF risk only among HF cases with ischemic origin [61]. In our study, AMI partly mediated the association between alcohol intake and HF [152, 153]. This may indicate that mechanisms other than the anti-atherosclerotic properties of alcohol may contribute to the protective association between alcohol intake and HF. However, we cannot rule out the possibility that the inverse association was mediated by unmeasured IHD.

5.3 THE BIOLOGICAL MECHANISMS BY WHICH LIGHT TO MODERATE ALCOHOL INTAKE MAY REDUCE THE RISK OF AMI AND HF

Several biological mechanisms have been proposed to explain the link between light-moderate alcohol intake and a lower risk of atherosclerosis. A large body of evidence shows that alcohol consumption is associated with an increased HDL cholesterol level in a dose-response manner [88, 96, 98, 99] and that almost 50% of the protective effect of light-

moderate alcohol consumption on IHD can be explained through its effect on HDL cholesterol [96, 98, 99]. On the other hand, a study from Norway, which pooled several large-scale cohorts including the HUNT could not confirm that HDL cholesterol is a major mediator for the association between alcohol intake and cardiac mortality [154]. However, it should be noted, that cardiac mortality usually has lower specificity than hospital-based AMI diagnoses which might explain the discrepancy between this and most other studies. The mediating role of HDL cholesterol in the association between alcohol consumption and the risk of HF is less certain than in IHD [10, 25, 103, 155]. According to interventional studies, moderate alcohol intake may elevate HDL cholesterol and apolipoprotein-A levels [20, 88, 91] by increasing the activity of lipoprotein lipase [96, 156] and decreasing the activity of cholesterol-ester-transfer protein [103, 157].

Light to moderate alcohol consumption is also associated with a better coagulation and fibrinolytic profile [96, 101, 103]. It may lower plasma fibrinogen and thromboxane-A levels and may inhibit platelet aggregation [18, 101]. Furthermore, moderate alcohol consumption may reduce the plasma concentrations of inflammatory markers, as C reactive protein and interleukin-6 [18, 88, 91, 100] and may improve endothelial function [76, 96]. Some studies suggest that the polyphenol content of alcoholic beverages in wine and beer may also have some additional anti-inflammatory effects [88, 90] and it may even modulate leukocyte adhesion [88, 90]. Light to moderate alcohol intake may improve insulin sensitivity and glycaemic control, most likely by increasing adiponectin production [20, 93, 96, 102-104]. Lastly, regular low-level alcohol intake may have a direct preconditioning effect on the myocytes which may contribute to the direct protective effect of low level alcohol intake on the myocardium [158]. It is also associated with a lower level of high-sensitivity cardiac troponin T, a marker of chronic subclinical myocardial damage [159].

5.4 METHODOLOGICAL CONSIDERATIONS

There are many sources of potential bias that could influence the results of observational studies concerning the link between alcohol consumption and CVD. In the following section, we discuss the strengths and limitations of our studies.

5.4.1 Study design

Study I, II and IV had prospective designs that help to eliminate reverse causation and minimise recall bias. In study III, the main limitation was the cross-sectional design, which restricts causal inference. However, in study III we were able to detect subtle subclinical changes in the LV function before LV dysfunction may have caused clinical symptoms. Experiencing clinical symptoms might make some individuals decrease their alcohol consumption.

5.4.2 Selection bias

Due to the low net migration rate in the county [160] the biased loss to follow-up had little threat to validity [113, 123]. The participation rate was very high in HUNT1, and though it

dropped progressively in HUNT2 and HUNT3, it remained relatively high. However, selective participation is considered to be a lesser threat to validity in cohort than in case-control studies [161]. In general, the participation rate was lower among men than among women and among those aged < 40 and > 80 years than among those aged 40-80 years. A non-participation study, conducted in a random sample of non-attendants in the HUNT2 population showed that the main reason for non-participation among younger and middle aged individuals was lack of time or leaving the county [160]. The general reason for non-participation among older individuals was that they already had regular health check-ups or that they had difficulties in going to the study centres due to health reasons [160]. A study which explicitly examined the non-response rate according to alcohol consumption categories found that abstainers were slightly more likely to be non-responders than individuals with other alcohol consumption habits [162]. The population of the Nord-Trøndelag county is socio-economically, ethnically and genetically homogenous, and the health-system in Norway is based on universal public insurance, providing similar high-quality service with equal accessibility to everyone independent of socio-economic status [113]. This makes it less likely that non-responders would substantially differ in variables that might affect our results considerably, however we cannot exclude, especially among older individuals, that a health-related selection mechanism influenced the participation.

5.4.3 Information bias

As in earlier studies using self-assessed information on alcohol, results might have been affected by a non-differential misclassification of the exposure. Self-reporting, which is the standard method to collect information on alcohol consumption in observational studies, tends to under-estimate alcohol intake in the higher categories, i.e., heavy drinkers systematically under-report their consumption [18, 25, 116, 163]. The effect of this systematic underreporting on the observed estimates might be twofold. First, it might classify some heavy drinkers into moderate drinkers, thus lowering the apparent threshold for harmful effect. Second, it may lead to an overestimation of the harmful effect or an underestimation of the protective effect among moderate drinkers.

As ascertainment of the outcome was independent of the baseline measurements, it is less likely that the value of the outcome would be influenced by the value of the exposure. However, we cannot rule out that in study II individuals with a known alcohol use disorder might have been more likely to receive a diagnosis of HF than individuals without a history of alcohol use disorder. This might lead to over-estimation of the harmful effect of alcohol intake on HF risk among problem drinkers. AMI and HF cases were identified from the hospital discharge records and the National Cause of Death Register. The overall validity and reliability of the hospital-based diagnoses are high in the Nordic countries [164-166]. The specificity of the AMI diagnoses in the Norwegian Patient Register is 99.7% [167]. The specificity of the causes of death in the National Cause of Death Register is lower due to the relatively low rate of autopsy [168]. However, our results remained mostly the same when we excluded cases that were obtained only from the National Cause of Death Register. In study

III, we used high sensitivity tissue Doppler echocardiographic method that can detect subtle changes in LV function with high accuracy [114]. In study IV, AF diagnoses were identified from hospital medical records, and all diagnoses were validated by experts to ensure high specificity [121].

5.4.4 Confounding

We could adjust for a large number of potential confounders including smoking, physical activity, BMI, marital status, education, anxiety, depression, or common chronic disorders. Furthermore, in Norway, the socioeconomic differences are among the lowest in the world [123, 169]. Moreover, the health care system is equally accessible for all citizens regardless of socioeconomic status, this might minimise differences in healthcare accessibility due to socioeconomic position [123]. The population in Nord-Trøndelag is relatively homogenous both genetically and ethnically.

One of the major strengths in our studies is that confounding due to social factors associated with alcohol consumption is likely to be lower than in studies conducted in other Western countries. Alcohol consumption is low in Norway by European standards, and it is unusually low in the Nord- Trøndelag County [118, 154]. Norway has a strict alcohol policy which includes high taxes on alcohol, limited availability of alcoholic beverages in state-owned shops, and an extensive public health effort to promote alcohol free-pubs, hotels, dance halls and restaurants [170]. Therefore, non-drinking is socially more accepted than in other Western societies [171]. Abstainers represent a considerably more healthy and socially less deprived group in Norway than in other countries, which reduces the likelihood of uncontrolled confounding by social pressure, social support and integration [172].

The “sick-quitter bias”, an important limitation in alcohol studies which did not assess previous alcohol intake can be described as a specific form of confounding by illness, where the exposure varies over time in response to changes in ill-health. One of the major strengths in our studies was the available information on alcohol consumption ten years before the baseline measurement. Therefore, it was possible to separate abstainers who were former drinkers from long-term abstainers.

5.4.5 Random error

Given the large sample size in our studies (studies I, II and IV), in general, we had a limited amount of random error. However, the distribution of specific variables, such as alcohol consumption was uneven. The majority of the participants reported consuming less than seven drinks per week which limited our possibility to draw conclusion regarding higher intake. In study III, the overall sample size was smaller, which further limited our possibilities to conduct subgroup analyses.

5.4.6 Generalizability

The distribution of different alcohol dehydrogenase gene variants has been shown to be different in Asia and Europe, [173, 174] These gene variants influence the speed of alcohol

metabolism, thus, our findings might not directly be generalizable to other ethnic groups, especially in Asian populations.

5.5 PUBLIC HEALTH IMPLICATIONS

Methodological problems that may limit casual inference cannot fully be avoided, but the consistency of the results, together with the supporting evidence from experimental studies, and the plausibility of biological explanations endorse the hypothesis that light to moderate alcohol intake may be protective for some CVD. As randomised control trials in this area are lacking, public health recommendations concerning alcohol consumption can only rely on observational study results. There is an agreement that the initiation of alcohol consumption among non-drinkers should be avoided due to the risk of alcohol use disorder [83]. However, concerning habitual moderate alcohol consumption, public health consensus is missing, and recommendations and guidelines vary greatly [83, 175, 176]. While the WHO has a “less is better” policy toward alcohol consumption [177], many guidelines, based on the evidence on its cardio-protection, recommends alcohol consumption in moderation, usually up to 7-9 drinks per week for women and 14 drinks per week and with a limitation of the amount on one drinking occasion [73, 82-84, 176].

One major argument in favour of the zero consumption policy is that it is not clear how moderate alcohol intake affects the risk of several other diseases [12]. There is some evidence showing that even one-two drinks per day for women and two-three drinks per day for men increases the risk of liver injury [18, 178]. While light to moderate amount of alcohol consumption is not associated with a higher risk of most cancer, it may increase the risk of breast cancer in women and colorectal cancer in men [179]. However, it is possible that the observed, slightly elevated risk among moderate drinkers is due to binge drinking, as this increased risk of breast cancer cannot be found among low-level frequent drinkers [180]. The European Code Against Cancer recommends a maximum of 20g per day (~two drinks) for men and 10g (~one drink) per day for women, but preferably no alcohol consumption at all [181].

Another major limitation of the recommendations is based on net harm and net benefit of alcohol consumption, that the effect of alcohol intake may differ between individuals or ethnic groups [12]. Studies in India could not detect a beneficial effect of light to moderate alcohol intake on IHD risk, but it is not clear whether the lack of association was due to genetic characteristics or due to cultural factors and drinking patterns [1, 10, 29]. Genetic polymorphism of alcohol dehydrogenase genes as ADH1C or ADH1B may be important effect modifier for the association between light to moderate alcohol intake and IHD risk [182-185].

Finally, the population for which alcohol intake seems to be the most beneficial, i.e., individuals over 50 years, is usually broadly medicated with antihypertensive drugs, statins and beta-blockers. There is insufficient evidence available regarding the possible interactions between moderate amount of ethanol intake and different pharmaceuticals.

Advising non-drinking to drinkers consuming alcohol within recommended limits, i.e., ≤ 7 drinks per week for women and ≤ 14 drinks per men without binge drinking [82] may not be

advocated due to the strong evidence that supports the protective effect of low level, frequent drinking [10]. Our results support the recommendation that alcohol policy should rather focus on discouraging people from binge drinking which appears to be harmful even if it is occasional or if the average intake remains light to moderate [1, 10, 18]. The improvements of other protective factors than moderate alcohol consumption, such as healthy diet and moderate physical activity should be even more emphasized, as these methods are less disputed [4].

5.6 CONCLUSIONS

In this thesis, we examined the association between light to moderate alcohol intake and the risk of AMI, HF and AF, while we could take care of some previous methodological shortcomings. We could confirm previous results that light to moderate alcohol intake was associated with a reduced risk of AMI and HF and a slightly increased risk of AF even when former drinking habits and confounding from several factors were taken into account. We found no evidence for a better LV function among light to moderate drinkers. When drinking pattern was taken into consideration, frequent low-level alcohol intake was associated with the lowest AMI and HF risk. Furthermore, the attributable risk of alcohol consumption within the recommended limits, i.e., \leq seven drinks per week for women and \leq 14 drinks per week for men with no reported binge and/or problem drinking was negligible in this low-drinking population. On the other hand, among binge- and or problem drinkers, even if the average consumption level remained low, alcohol consumption was associated with slightly increased HF risk and a subtle sign of cardiac remodelling compared to abstainers. Our findings indicate that alcohol consumption within the recommended limits may provide some benefit on cardiovascular health.

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