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Atrial fibrillation and its relation to alcohol consumption in the general population: The seventh survey of the Tromsø Study

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ABSTRACT

Background: Atrial fibrillation (AF), the most prevalent cardiac arrhythmia, characterized by disruption of the electrical activity in atria, leading to the cardiac rhythmic disorder. Alcohol consumption has dose-dependent relationship with cardiovascular diseases and considered as a contributing factor for incidence of AF. Epidemiological studies have consistently shown a dose-dependent relationship either linear or J-shaped between alcohol consumption and the risk of AF incidence. Sex differences in the relationship between alcohol consumption and AF have been documented in various studies. This study primarily aims to investigate the sex-specific associations between alcohol consumption and the incidence of AF.

Aim: The objective of this study is to explore the relationship between alcohol consumption and incidence of AF among men and women in the 7th survey of the Tromsø study.

Material and Methods: This population-based longitudinal cohort study using data from Tromsø7 (2015-2016). All inhabitants aged 40 years and older in the Tromsø municipality (n = 32,591) were invited to participate. A total of 21,083 participants aged between 40 and 99 attended the survey, resulting in a participation rate of 64.7%. Complete case analyses were performed, and the final cohort consisted of 17243 participants among these 8,280 were men and 8,963 were women. Physical examination was conducted within municipality and alcohol variables and potential confounders were assessed by using a comprehensive questionnaire (Q1). Statistical analyses were performed using IBM SPSS. Descriptive statistics were used to present continuous variable as means (SD) and categorical variables as proportions. To examine the association between alcohol consumption (including drinking patterns and alcohol) and incidence of AF, Cox proportional hazards regression analysis was utilized to calculate hazard ratios (HRs) with 95% CIs. All analyses were conducted with a focus on sex differences.

Results: The sex-stratified Cox regression analysis revealed a positive association between alcohol consumption and the incidence of AF. In men, the HRs for moderate and heavy alcohol consumption were 1.28 (95%CI: 1.01-1.64) and 1.84 (95%CI: 1.29-2.61), respectively, based on alcohol frequency. Similar associations were observed for consuming 3-4 drinks per

occasion in adjusted models, with HRs 1.31 (95%CI: 1.02-1.66) and 1.30 (95%CI: 1.02-1.67). There were no associations found in women.

Conclusion: The findings indicate a positive relationship between alcohol consumption and an increased AF risk in men; however, no such association was identified in women. To comprehend the underlying mechanisms of sex differences, more research studies are recommended.

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ABBREVIATIONS

AF	Atrial Fibrillation
BMI	Body Mass Index
BP	Blood Pressure
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
Cm	Centimetre
ECG	Electrocardiogram
ESC	The European Society of Cardiology
g	grams
g/day	grams/ day
GBD	Global Burden of Disease
HRs	Hazard Ratios
ICD	International classification of Diseases
kg	Kilogram
L	Litre
m^2	square meter
ml	Millilitre
Q1	Questionnaire 1
SAUs	Standard Alcohol Units
SD	Standard Deviation
UNN	University Hospital of North Norway
USA	United State of America
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Atrial Fibrillation

Cardiovascular diseases are the leading cause of death worldwide [1]. Atrial fibrillation (AF) is the most prevalent type of cardiac arrhythmia (irregular heartbeat) and has become a significant medical concern, affecting around 20 million people globally [1]. AF is characterized by a disruption in the electrical activity of the upper chambers (atria) of the heart, leading to a rhythmic disorder that can be identified through an electrocardiogram (ECG) [2]. AF can manifest in several forms:

- Paroxysmal AF: Episodes that start suddenly and stop spontaneously within 7 days or with medical intervention.
- Persistent AF: Episodes that last longer than 7 days and require intervention to terminate.
- Permanent AF: When both patient and clinician decide to stop attempts at rhythm control [3].

Common symptoms include dizziness, fast heartbeat, fatigue, chest pain, and shortness of breath, these symptoms often exacerbated in individuals with pre-existing heart conditions [4, 5]. The management of AF is complicated and requires a holistic and multidisciplinary approach, focusing on controlling risk factors that may increase the likelihood of developing AF [3, 4]. However, some patients may be asymptomatic, making diagnosis challenging. The importance of AF prevention and management cannot be overstated due to its serious complications. AF significantly increases the risk of stroke (up to 5 times), heart failure, and premature death. It is also associated with reduced quality of life, increased hospitalizations, and substantial health-care costs [6].

1.1.1 Epidemiology of AF

The incidence and prevalence of AF has been increased by three times over the past 50 years, due to an aging population and the presence of cardiovascular conditions among older individuals [7, 8]. The Global Burden of Disease (GBD) estimates that the AF prevalence is currently around 47 million and still increasing worldwide [9]. In 2010, the AF prevalence was around 06 million in the USA and 9 million in Europe and there is an estimation that it will be increased to 16 million (in USA) and 17 million (in Europe) by 2050 [9]. Prevalence varies significantly by age, ranging from 2% in the general adult population and reaching approximately 12% in people aged 80 years or older [7]. In Norway, the AF prevalence among adults (aged ≥18 years) stands at 3.4% [10] which is among the highest in the world, with 2.8% in women and 4.0% in men [10]. The age-standardized incident rates of AF in Norway (1990-2017) have shown an increase of 22.3%, in contrast to trends in most Western European countries, where rates have decreased [11]. The AF incidence rates based on entire Norwegian population (2004-2014) indicate the more stable incidence trends, particularly among women [10]. In addition, findings from the Tromsø Study (1994-2016), indicate a decrease AF incidence among women and an increase among men, following a reversed U-shaped pattern [12].

1.1.2 Risk Factors of AF

Various risk factors contribute to the development of AF, which can be categorized into non-modifiable and modifiable risk factors. Non-modifiable risk factors include age and sex, while modifiable risk factors encompass obesity, hypertension, alcohol consumption, diabetes, congestive heart failure, sleep apnea, smoking, physical activity [3, 7], and psychological factors [13].

1.1.2.1 Non-modifiable risk factors

- Age: A significant risk factor of developing AF, increasing substantially in older populations [14]. Elderly individuals (over 65 years) often present AF alongside serious conditions such as chronic heart failure, coronary artery disease, dementia (loss of memory), and stroke as compared to young individuals [15].

- Sex: Men have 30% to 70% higher rate of AF incidence compared to women, although the lifetime risk is similar for both sexes [13].
- Genetic predisposition: Both monogenic and polygenic factors have been identified as contributing to the risk of AF [15].

1.1.2.2 Modifiable risk factors

Given the multifaceted nature of AF and its associated risk factors, a comprehensive approach to prevention and management is crucial. This includes lifestyle modifications such as weight loss, blood pressure management, daily exercise with a balanced diet, all of which may reduce the risk to develop AF and improve overall cardiovascular health.

- Hypertension: This condition elevated the AF risk by 1.7 to 2.5 times [13].
- Obesity: A significant contributor to AF risk due various pathophysiological mechanism linking obesity and AF [13].
- Diabetes mellitus: This condition increases the AF risk by 1.28 times [13].
- Sleep disorders: Obstructive sleep apnoea, also associated with prevalence of AF ranging from 21% to 74% [13].
- Alcohol consumption: There is a dose-response association between alcohol consumption and risk of AF [16].
- Smoking: A strong dose-response association exists between smoking and risk of AF, particularly among current smoker [13].
- Physical activity: Leisure time (physical activity) exhibits J-shaped relationship with AF risk [17].
- Psychological factors: Mental health disorders and stress also contribute to the risk of developing AF [13].

Therefore, research studies demonstrated that the proper identification of AF and its risk factors along with implementing appropriate preventive measures and lifestyle modifications can lead to a significant decline in the incidence of AF. These interventions not only enhance the quality of life but also alleviate the burden on healthcare systems [2].

1.2 Alcohol Consumption

Alcohol consumption is significant contributor to the GBD , health loss and mortality [18]. The GBD study defines this burden as the impact of health problems on a population, measured by financial costs, mortality, morbidity, or other indicators. The impact of alcohol on health is multifaceted and dose dependent [5] . According to Manthey et al, the global consumption of alcohol (pure ethanol) has been steadily increasing since 1990, from 5.9 L per person to 7.6 L per person in 2030 [19, 20]. The World Health Organization (WHO) reports on the average amount of pure alcohol consumed worldwide in 2016 was 6.4 L per person aged 15 and over [21].

However, this figure masks substantial regional variations; Europe has the highest per capita consumption while the Eastern Mediterranean region has the lowest [21]. In Norway, alcohol consumption use has increased significantly among older populations, over the past three decades, indicating that the age and sex disparity in alcohol use in Norway is narrowing [22]. In Norway, alcohol consumption per capita, measured in L pure alcohol (aged 15 and over), increased from about 5 L in the 1960s to approximately 7 L in recent years, although this remains lower than the European average [23].

Measuring alcohol consumption presents challenges due to variations in drink sizes, alcohol content, and self-reporting biases. Standardized methods have been developed to quantify consumption, including the use of standard alcohol units (SAUs). One SAU includes 12 grams (g) of pure ethanol, which is about the same as 120 millilitres (ml) of wine, 330 ml of beer, or 40ml of spirits in many countries [16, 19]. Men and women should consume less than 100g of alcohol per week, in accordance with guidelines on cardiovascular disease prevention in clinical practice by the European Society of Cardiology (ESC) [24]. According to US Dietary guidelines for Centers for Disease Control and Prevention (CDC), the daily recommended alcohol consumption for men should be 2 drinks and for women 1 drink or less [19, 25].

1.3 Alcohol Consumption and AF

Generally, it is accepted that regular consumption of alcohol (acute and chronic) has dose-dependent relationship with cardiovascular diseases (14) and considered as a contributing factor for incidence of AF [26]. A dose-dependent relationship (either J-shaped or linear) between alcohol consumption and AF incidence risk has been repeatedly demonstrated by epidemiological studies [26]. Acorrding to comprehensive research, the incidence of AF risk increased by 6-8% for each drink consumed per day, and even moderate levels of alcohol

consumption with different drinking patterns have association in the development of AF with high risk [19, 27]. A high risk of AF was associated to a regular consumption of 1.2 drinks per day [16].

Notably, a meta-analysis from UK Biobank found that any amount of alcohol (1 drink per week) was strongly related to a higher risk of AF [28]. Specifically, heavy and moderate alcohol consumption increases AF incidence by 30% and 12% respectively, although low alcohol consumption did not [29]. Various alcoholic beverages-based analyses demonstrated that their effects on AF risk do not significantly differ among spirits, wine, and beer [16, 26].

1.4 Existing knowledge on Alcohol Consumption and AF

Extensive research has explored the complex correlation between alcohol consumption and AF, highlighting substantial variations depend on different drinking patterns [18]. Based on current research and knowledge, the chronic consumption of alcohol has detrimental effects on cardiovascular conditions and associated with a higher risk of AF [1]. Excessive alcohol intake is associated with several cardiovascular diseases, including hypertension, which further increase the likelihood of AF incidence [30]. Interestingly, moderate consumption may have some beneficial effects on cardiovascular health in certain populations [16].

1.4.1 Drinking Patterns

Current knowledge indicates that drinking patterns such as moderate, heavy and binge drinking can have significant impact on risk of AF incidence [30]. Drinking patterns, particularly binge drinking, are associated with increased AF risk [25]. The concept of "holiday heart syndrome," describes the phenomenon where AF is induced by acute excessive alcohol consumption, was first described by Ettinger et al. in 1978 and has been supported by subsequent research [25].

In the historical context, evident by finding that approximately 60% of individuals have AF frequently consume high quantities of alcohol during weekends (binge drinkers) [31] and this pattern has been associated with the phenomenon known as "holiday heart syndrome [32].

Further investigation through Norwegian health examination surveys, demonstrated that moderate (1-2 drinks daily) and high alcohol consumption (2 or more drinks daily) are associated to an 18.0% and 25.0% increased AF risk, respectively, when compared to low intake of <1drink per week. Conversely, consumption of <1 drink per day had no significant association with an increased AF risk [33]. It is also found that heavy alcohol intake (>35

drinks per week in men and 14 drinks per week in women) can lead to 2.3 times higher risk of AF when compared to non-drinker [26]. A meta-analysis indicates that consuming ≥12g alcohol daily significantly increased the incidence of AF risk [34] and supporting a linear dose-response relationship across various drinking patterns even at small doses [16]. Furthermore, for individuals who consumed 1-6 drinks per week, there is no notable increase in AF risk compared to current drinkers who took less than 1 drink weekly [31]. Likewise, the Norwegian HUNT Study also reported that both men and women had high risk of AF with heavy alcohol consumption but there was little to no association were found (<1 drink in women and <2 drinks in men per day) [35]. A dose-response association of alcohol intake and AF indicated that the prolonged use of alcohol and AF risk may not significantly vary by sex [31].

1.4.2 Types of Alcohol

The type of alcoholic beverage consumed has also been a focus; some studies suggest that beer may have a more harmful association with AF risk compared to wine or spirits, while others had not described a notable differences between beverage types [19]. Some studies proposed that beer can have a more detrimental impact on AF risk in comparison to wine or spirit, although evidence remains mixed across research.[19]. Another dose-dependent study by Biddinger K.J. demonstrated that 1 drink of alcohol per week, can increase the risk of AF significantly [28], consistent with findings that regular alcohol consumption even at smallest doses can increase the risk of AF in case of beer and spirits [16]. Research exploring the effects of different types of alcohol (wine, spirits and beer) explored J-shaped relationship in those who consumed wine but not beer and spirits [18]. In addition, dose of alcohol consumption <7 drinks weekly, associated with less risk of AF in wine and spirit but beer had harmful impact at any amount [36].

1.4.3 Sex Differences

Sex differences in the alcohol-AF relationship have been observed in several studies and generally, women consume less alcohol as compared to men [19]. For men, moderate alcohol consumption considerably raise the probability of AF risk, but not for women [29, 37], while both men and women have association with the high AF risk on heavy consumption of alcohol [19, 29]. Any amount of alcohol consumed can increase the risk of AF incidence, but for women, consuming >1.4 drinks per day may up the risk of AF [27]. Various research studies have not demonstrated that women across any level of alcohol consumed, has association with

high AF risk [19]. Even , most of previous research include only a limited number of women who had excessive/heavy alcohol consumption [19]. A meta-analysis study examined a linear relationship between alcohol use and risk of AF incidence among men who are more susceptible to develop the AF at low doses of alcohol as compared to women, showed J-shaped relationship on heavy alcohol consumption [19]. There were no significant sex-differences in alcohol-related risks of AF but types of alcohol such as beer has harmful association with AF risk, while wine (8 drinks per week) and spirits (3 drinks per week) had no detrimental effects [36], reported by a prospective study conducted on sexes.

However, sex related difference in relationship of alcohol and AF may be due to psychological and social behaviours because women who consumed alcohol had more controlled drinking habits as compared to men. In addition, sex related alcohol metabolism and interactions of hormones may be responsible for such differences [29]. A study by Johansson et al. highlighted sex-specific differences, revealing that women have not shown a notable association between alcohol consumption and risk of AF. In contrast, men only exhibited a significant increase in AF risk when consume ≥ 4.83 standard drinks per week [38].

1.4.4 Pathophysiological Mechanism

Pathophysiological mechanisms underlying the association between alcohol use and AF are complex and multifactorial [26], but alcohol may exhibit proarrhythmic effects [19]. The potential pathophysiological mechanisms are triggered by acute alcohol consumption such as:

- Cellular effects: Oxidative stress and inflammation.
- Autonomic effects: Reduced heart rate variability and vagal trigger.
- Electrophysiological effects: Multiple disorders and dysfunction of ion channels in the myocardium [19, 26].

The atrial remodeling (changes in structure and functions of atria such as alcoholic cardiomyopathy) and interactions with several risk factors (hypertension, diabetes, smoking and obesity) are associated with chronic alcohol consumption, leading to AF incidence [16].

Although, the impact of alcohol on the atria is dose-dependent; for instance, individuals who consumed 8-21 drinks per week exhibit notable alterations in both the electrophysiology and structure of the heart, which may induce risk of AF [29, 39]. Another dose-related meta-analysis demonstrated that the alcohol intake and AF risk association has been shown to be positive and non-linear [29].

Therefore, a modest rise in risk at lowest levels of alcohol consumption result in a little increase in the AF risk, but when intake exceeds approximately 40 grams per day (g/day), the increase becomes more noticeable [29] and alcohol consumption at this level marks a threshold beyond which the detrimental effects of alcohol may become more pronounced, potentially leading to significant harm to the electrophysiological system of the heart [29].

Current understanding of the relationship between alcohol intake and AF, highlights a significant gap in knowledge regarding the dose-response relationship. Some studies have suggested that low and moderate alcohol consumption may have a protective effect on cardiac health [30], and others demonstrated a direct association between low and moderate alcohol consumption and the incidence of AF [34, 40, 41]. The existing literature presents conflicting evidence impact of low and moderate alcohol consumption on risk of AF, required further investigation to overcome these discrepancies. Research studies have focused on the pathophysiological mechanisms, including electrophysiological and structural alterations in the heart, related to alcohol consumption and AF [19] However, the relationship between these documented structural changes, and specific dose of alcohol are not defined and specified in men and women [31].

However, the significant insights of various studies demonstrated the variations in specific dose, duration, types of alcohol and frequency, are due to individual differences in alcohol consumption (susceptibility to alcohol effects on AF incidence). Furthermore, it is also evident from research that the exact amount of alcohol consumption is underestimated (not established as its quantity were self-reported by the participants) especially in women which is the major limitation in many studies [1].

This study investigates the association between alcohol consumption and the incidence of AF in the Norwegian population with an emphasis on sex differences, addresses important knowledge gaps in the existing literature. To explore sex-specific difference, future research should focus on how alcohol consumption influences incidence of AF in men and women, along with the dose-response relationship assocaited with various levels of alcohol consumption such as light, moderate, and heavy and the risk of AF, can provide insights into the possible sex-specific differences [10, 42]. Finally, by emphasizing the necessity, it could support and educate clinical guidelines and public health recommendations regarding alcohol consumption to mitigate AF risk.

1.5 Research Question

What is the sex-specific association between alcohol consumption and the incidence of AF in the Norwegian population?

1.6 Research Objectives

The main purpose of this study is to investigate relationship between alcohol consumption and incidence of AF among men and women separately in Norwegian population cohort. The specific objectives are:

- To examine the AF incidence across different levels of alcohol consumption among men and women.
- To assess the association between various drinking patterns of alcohol (e.g., alcohol frequency and alcohol drinks) and incidence of AF, stratified by sex.
- To evaluate the impact of potential confounders on the association between alcohol consumption and AF incidence, including body mass index (BMI), presence of hypertension, smoking status, physical activity, and educational level.

1.7 Hypothesis

There exists an association between alcohol consumption and incidence of AF in both men and women in the Norwegian population, with the strength of this association differing between sexes. The lower alcohol consumption is associated to a lower risk of AF, and conversely, the higher alcohol consumption is associated with an increased risk of AF for both men and women.

CHAPTER 2

MATERIAL AND METHODS

2.1 Study Design

The present cohort study utilized the data from 7th survey of the Tromsø Study (Tromsø7). Participants were followed-up for the incident AF. All the participants were identified, who have emigrated or died (during follow-up) from the Tromsø municipality, were registered to the National Population Register [43].

2.2 Study Population

Tromsø, the largest city in Northern Norway having 77,000 inhabitants approximately [44]. The Tromsø Study is population-based longitudinal cohort study that have been conducted in the Tromsø municipality Norway. The main objective of this study was to identify the underlying causes of elevated mortality due to cardiovascular diseases and to identify strategies for the prevention of stroke and heart attack. The study comprised of seven surveys conducted between 1974 to 2016. It includes subjects who have attended at least one of the seven surveys [45]. In present study, from Tromsø7 (2015-2016) has been used [45]. In Tromsø7, 16052 men and 16539 women aged 40-99 years, were invited (**Appendix-1**) to participate. In total, 10, 009 men and 11, 074 women accepted the invitation (average attendance 64.7%) [45, 46]. A total of 21,069 participated, in the study and completed baseline examination and questionnaire.

2.3 Inclusion/ Exclusion Criteria

The inclusion and exclusion criteria were used to ensure the integrity of the study and its emphasis on incident AF cases.

2.3.1 Inclusion criteria

- Participants in the study should be 40 years of age or older and residents of Tromsø municipality.
- Provided informed consent to participate in the study.
- Completed the baseline questionnaire and health examination.

2.3.2 Exclusion criteria

- Individuals with suspected AF but without a confirmatory ECG record.
- Participants with a prior diagnosis of AF at the start of the Tromsø7.
- Participants who emigrated before the start of Tromsø7.
- Individuals who did not provide consent for medical research.
- A total of 14 individuals were excluded from the dataset for this reason.

Participants with missing information on alcohol variables (drinks per occasion and frequency) and potential confounders such as BMI, systolic blood pressure (BP), diastolic BP, antihypertensive drugs, education level, smoking status, physical activity were excluded from this study [16]. For the variables sex and age, there were no missing values. Complete case analyses were performed. Only complete cases were included in the analysis, and missing variables were excluded. The inclusion/exclusion criteria of study population presented in flowchart (Figure 1).

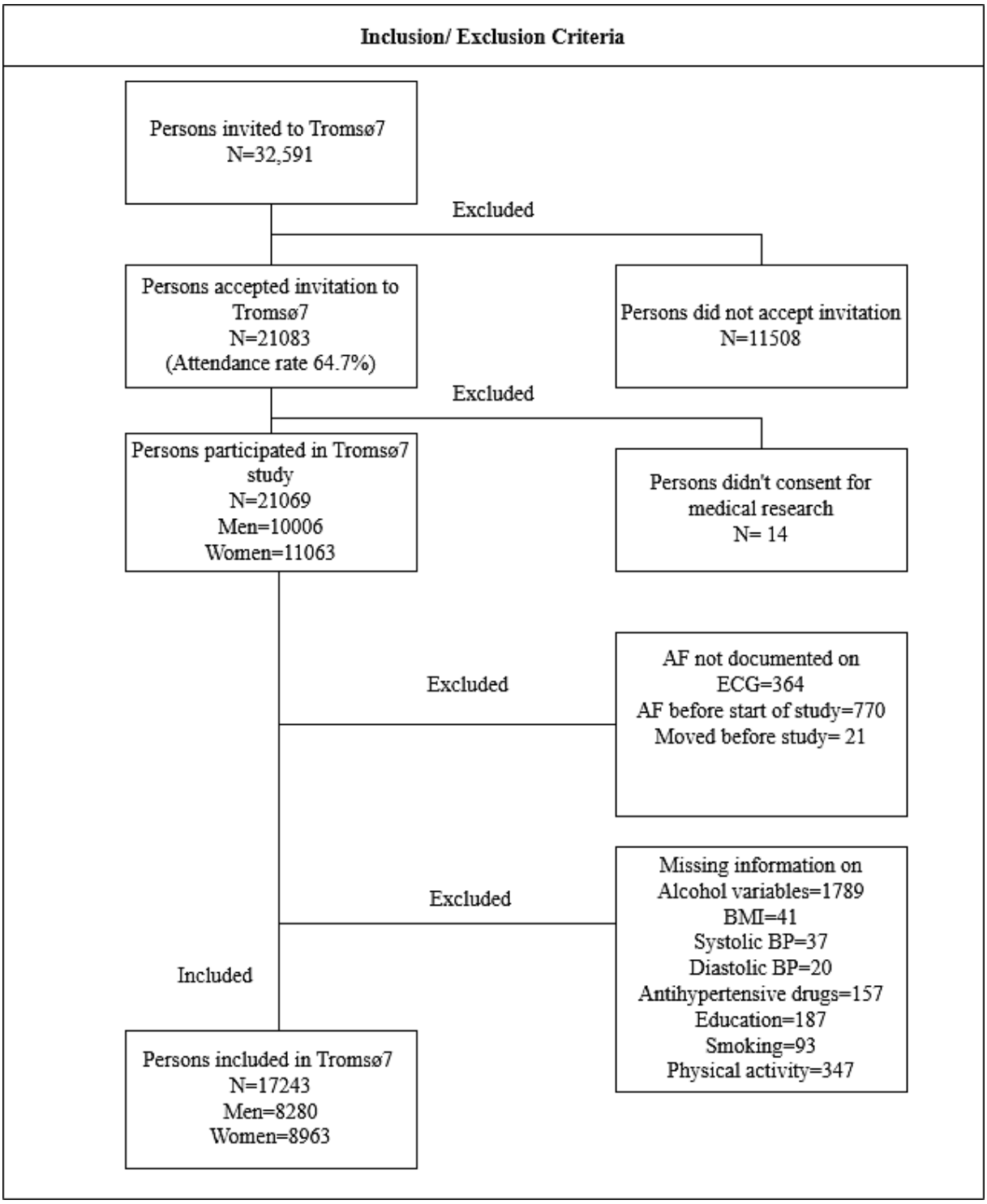

Figure 1: Inclusion/Exclusion Criteria for Study Population

2.4 Ethical Considerations

The Regional Committee of Medical and Health Ethics North has approved the Tromsø7 (reference 2014/940). Each participant gave written informed consent at attendance time. The Norwegian Data Protection Authority has approved the data which was collected securely, and evaluated [45]. The dataset in this study was anonymized that did not require separate approval from Regional Ethics Committee (REK).

2.5 Data Collection

2.5.1 Baseline Examination

The data collection for the Tromsø7 involved a comprehensive health examination and a detailed questionnaire (Q1) (**Appendix-2**). The health examination was conducted by trained personnel at the study site. The baseline examination included the following components discussed below.

2.5.1.1 Anthropometric measurements

Participants with light clothing and no shoes, and their height was measured using a wall-mounted stadiometer to the nearest 0.1 centimetre (cm) and the weight was recorded with electronic scales to the nearest 0.1 kg. BMI was calculated by the weight in kg divided by height in meters squared (kg/m^2).

2.5.1.2 BP measurements

Three BP readings were taken using an automated device (Dina map ProCare 300) at one-minute intervals. Analysis was done using the mean of the second and third readings.

2.6 Variables Used in Analyses

An invitation which includes a comprehensive questionnaire was distributed to all participants via mail prior to their baseline examination. All questionnaires full version (in English and Norwegian) of Q1 were available at webpage of the Tromsø study (https://uit.no/research/tromsostudy). Participants were asked to complete the questionnaire at home and bring it to their examination appointment. Q1 covers social demographic aspects,

disease conditions, lifestyle, and medication use [45]**.** The multiple variables used in the analyses were obtained from Q1 in Tromsø7.

2.6.1 Alcohol Variables

In this study, the main exposure variable is the alcohol consumption g/day were assessed as drinking patterns (alcohol frequency and drinks per occasion) and types of alcohol (beer, wine, and spirits). The alcohol consumption was categorized as:

- Non-drinkers: 0 g/day
- Light drinkers: <12 g/day
- Moderate drinkers: 12 to <24 g/day
- Heavy drinkers: ≥24 g/day

The variable alcohol frequency assesses how often participants consume alcohol, ranging from,

- Never drinkers (who never drink alcohol).
- Light drinkers (monthly/less frequently and up to 2-4 times a month).
- Moderate drinkers (2-3 times a week).
- Heavy drinkers (4 or more times a week).

The variable number of drinks (1 glass of beer, wine or spirit) quantify the drinks consumed per occasion, ranging from 1-2 drinks, 3-4 drinks and 5 or more drinks (≥5 drinks) (combination of 5-6, 7-9, and 10 or more drinks). Participants were asked to describe about quantity of alcohol consumed as wine (120 ml), beer (330ml) and/ or spirits (40ml), all contain 12g of pure ethanol. These types of alcohol such as beer, wine and spirits were further categorized into never drinker, light, moderate and heavy consumption of alcohol by types.

2.6.2 Covariates and Potential Confounders

Sex was used as a binary variable (male/female) and age was measured in 10 years groups. All analyses were performed separately for sexes. Several following variables were considered as potential confounders.

2.6.2.1 BMI

BMI was categorized as in dataset.

- Underweight to normal weight: 0-25kg/m²
- Normal to overweight: 25-30 kg/m²
- Obese: 30-Inf kg/m²

2.6.2.2 Physical Activity

Leisure time physical activity was measured by asking that *"Describe your exercise and physical exertion in leisure time over the last year"* and were categorized as:

- Sedentary: Reading, watching TV/screen or other sedentary activity.
- Light: Walking, cycling, or other forms of exercise at least 4 hours a week.
- Moderate: Participation in recreational sports, heavy gardening, snow shoveling etc. at least 4 hours a week.
- Vigorous: Participation in hard training or sports competitions, regularly several times a week.

2.6.2.3 Smoking Status

Participants asked about "*Do you/did you smoke daily?"*. In the analyses "yes, now" was considered current smokers and "yes, previously" as former smoker and "never" was treated as not current smokers.

- Never: Not current smoker
- Former smoker: "yes, previously"
- Current smoker: "yes, now"

2.6.2.4 Education Level

Education level of participants was measured by asking that *"What are the highest levels of education you have completed?"* with four categories,

- Primary/partly secondary education (Up to 10 years of schooling).
- Upper secondary education: (a minimum of 3 years).
- Tertiary education, short: College/university less than 4 years.

- Tertiary education, long: College/university 4 years or more.

2.6.2.5 Hypertension

Hypertension**,** defined as systolic BP ≥140 mmHg, or diastolic BP ≥90 mmHg, or use of antihypertensive medications [16, 47].

2.7 Follow-up and Detection of AF incident

Participants in this study followed-up from the date of their physical examination until either the date of their first reported case of AF, censored date due to emigration or death, or end of follow-up period on December 31, 2021, whichever occurred first. Individuals who had emigrated or died during follow-up period were identified using Population Register of Norway.

The identification on potential incident cases of AF was linked to the diagnosis registry (including diagnosis from all in-patients, and out-patient clinics) of the University Hospital of North Norway (UNN) (only hospital in this area) and to the Norwegian Cause of Death Registry. Further, all identified cases were selected for validation by using the International Classification of Diseases (ICD), 9th Revision (ICD–9) codes 427.0 to 427.99 and ICD, 10th Revisions (ICD-10) 147-I48 codes which are considered indicative (diagnostic codes) for AF incidence. In addition, medical hospital records were searched manually or electronic text in papers (used until 2001) for information on AF (for participants with cerebrovascular/ cardiovascular events). By following a detailed protocol and using medical hospital records, all the identified cases were validated by independent endpoint committee [12, 16, 47-49]. All the AF cases were considered confirmed when documented through an ECG. In addition, all the cases after 2016, and all the cases in those individuals who have not attended previous surveys were not validated. We just collected information on those from UNN diagnosis register, and they are not validated.

2.8 Statistical Analyses

IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Microsoft Word was used to produce the data (tables), flow chart created in the webpage (www.drawio.com). Results with a significance level < 0.05 were considered

significant for all analyses, and the statistical tests were two-sided. 95% confidence intervals (CIs) were provided for estimates. All statistical analyses were sex specific.

2.8.1 Descriptive Analysis

Characteristics (baseline) of the study population described by using descriptive statistics in which continuous variables as means with standard deviations (SD) and categorical variables as absolute frequencies and proportions (%) were prevented. The distribution of alcohol consumption patterns, alcohol types and the incidence of AF were visualized using tables.

2.8.2 Survival Analysis

The primary analysis employed Cox proportional hazards regression to compute hazard ratios (HRs) and 95% CIs to examine the association between alcohol consumption (drinking patterns and types of alcohol) and AF incidence which is sex- stratified. The survival time (time-to-event) was defined as the time from baseline examination to the date of AF diagnosis, death, emigrated or end of follow-up, whichever came first. The basic form of the Cox proportional hazards model is:

$$h(t) = h_o(t) \times exp(\beta^1 X^1 + \beta^2 X^2 + \ldots + \beta_p X_p) \quad (1)$$

where:

- $h(t)$ is the hazard function at time t
- $h_0(t)$ is the baseline hazard function
- $X_1, X_2, \ldots, X_p$ are the predictor variables
- $\beta_1, \beta_2, \ldots, \beta_p$ are the coefficients estimated from the data

Sex-specific HRs with 95% CIs for AF were estimated by multivariable Cox proportional hazard regression models.

- Model 1: Crude(unadjusted) model with alcohol variables (alcohol frequency, drinks per occasion and types of alcohol) as the sole predictor.
- Model 2: Adjusted for age.
- Model 3: Further adjusted for age, BMI, hypertension, smoking status, educational level, and physical activity.

In unadjusted model, the alcohol frequency, drinks per occasion and types of alcohol were examined as sole predictor for the risk of incidence of AF. In adjusted models, first adjusted alcohol frequency, types and alcoholic drinks per occasion with age and second adjusted with age and all potential confounders such as BMI, systolic BP, diastolic BP, hypertension, used of antihypertensive drugs, smoking, education level and physical activity. In addition, sensitivity analysis was done adjusted with age, potential confounders, alcohol types and total consumption of alcohol g/day. HR above 1, describes increased risk and below 1 describes decreased risk/protective effect. Participants who never consumed alcohols were excluded for further analysis for alcoholic drinks per occasion and types of alcohols. Light drinkers were used as the reference group with alcohol frequency, and drinks per occasion. never drinkers were used as the reference group for types of alcohol. The interaction analysis was done to examine whether sex modifies the association between alcohol variables and risk of AF, by including an interaction term (cross-product term) in the models [47]. The proportional hazards assumptions in the Cox models were evaluated in graphical assessment.

CHAPTER 3

RESULTS

3.1 Characteristics of the Study Population

The final cohort comprised of 17,243 participants, including 8,280 men and 8,963 women, reflecting a sex distribution of approximately 48% men and 52% women. During the follow-up period of 5.6 years, 493 individuals (2.9%) were diagnosed with AF (Table1). Among these cases, 324 (3.9%) were men and 169 (1.9%) were women, indicating that men had a higher risk of developing AF. The age distribution results indicated that the largest proportions, approximately 33.9% were within 40-49 years age group, followed by 30.7% in the 50-59 years group (Table 2). In contrast, older aged groups accounted for 24.2% in the 60-69 years category and 11.2 % in those aged 70 years and above. Regarding BMI, 23.3% of men and 41% of women had a BMI in the normal range (0-25), while 25.1% men and 21.7% women were as obese.

A total of 4,703 individuals (27.4%) in the cohort diagnosed with hypertension. Among these 2,689 (32.5%) were men and 2,014 (22.5%) were women. A significant proportion of participants,78.3%, were never used antihypertensive drugs, while approximately 19.2% were the current user of drugs. Regarding smoking status, 42.3% of men and 40.4% of women identified as never smokers. Current smokers comprised 13.5% of men and 14.7% of women, while former smokers accounted for 44.2% of men and 44.9% of women.

The education levels among participants varied considerably. A total of 3,465 participants (20.1%) completed primary or secondary education, while 4,859 (28.2%) attained upper secondary education. The largest group, comprising 8,919 participants (51.7%), had completed college or university education (both tertiary short and long). Among men, 4,048 (49.9%) and among women, 4,871 (54.3%) had the highest education level in college or university. In terms of physical activity, women demonstrated a breakdown of 12.6% engaged in sedentary, 65.6% in light activities, 19.3% in moderate activities, and 2.5% in vigorous training. While men indicated 14.7% sedentary activity, 50.0% light activity, 31.2% moderate activity, and 4.1% vigorous training (Table 2).

Table 1: Number of AF Cases in Men and Women

Number of af cases						
AF	**Total**		**Men**		**Women**	
	N 17243		N 8280	% 48.0	N 8963	% 52.0
No	16750	97.1	7956	96.1	8794	98.1
AF Confirmed	493	2.9	324	3.9	169	1.9

Table 2: Descriptive Baseline Characteristics of the Men and Women

Variables	**Total**		**Men**		**Women**	
	N	%	N	%	N	%
Sex	17243		8280	48.0	8963	52.0
Age (Years)						
• 40-49 • 50-59 • 60-69 • ≥70	5844 5286 4176 1937	33.9 30.7 24.2 11.2	2796 2461 2023 1000	33.8 29.7 24.4 12.1	3048 2825 2153 937	34.0 31.5 24.0 10.5
Body Mass Index (kg/m²) (%)						
• 0-25 • 25-30 • 30-Inf	5603 7614 4026	32.5 44.2 23.3	1932 4266 2082	23.3 51.5 25.1	3671 3348 1944	41.0 37.4 21.7
Hypertension (%)						
• No • Yes	12540 4703	72.7 27.3	5591 2689	67.5 32.5	6949 2014	77.5 22.5

Antihypertensive Drugs (%)						
• Never Used • Currently • Previously, not now	13502 3312 429	78.3 19.2 2.5	6308 1777 195	23.3 51.5 25.1	7194 1535 234	80.3 17.1 2.6
Blood Pressure Mean (SD)						
• Systolic BP • Diastolic BP	128.46 (18.99) 75.51 (10.02)		132.16 (17.61) 78.53 (9.66)		125.04 (19.58) 72.72 (9.52)	
Smoking Status (%)						
• Never • Current • Former	7127 2437 7679	41.3 14.1 44.5	3505 1119 3656	42.3 13.5 44.2	3622 1318 4023	40.4 14.7 44.9
Education Level (%)						
• Primary/secondary • Upper secondary • Tertiary, short • Tertiary, long	3465 4859 3449 5470	20.1 28.2 20.0 31.7	1669 2563 1796 2252	20.2 31.0 21.7 27.2	1796 2296 1653 3218	20.0 25.6 18.4 35.9
Physical Activity (%)						
• Sedentary • Light • Moderate • Vigorous	2347 10018 4311 567	13.6 58.1 25.0 3.3	1214 4143 2582 341	14.7 50.0 31.2 4.1	1133 5875 1729 226	12.6 65.6 19.3 2.5

Note: Mean (SD) for continuous variables and proportions (%) for categorical variables.

A comprehensive analysis on alcohol consumption among study participants, categorized by alcohol frequency, drinks per occasion and types of alcohol presented in Table 3. The data revealed that proportion of individuals, approximately 16 men (0.2%) and 47 women (0.5%) were never drinking alcohol. Among those who consumed alcohol, light drinking was the most prevalent pattern, with 63.7% of men and 69.9% of women categorized as light drinkers. Moderate drinking followed, with 28.6% of men and 24.2% of women identified as moderate drinkers. While only 7.4% men and 5.3 % women were heavy alcohol drinkers. When the drinks per occasion were examined, the majority reported consuming 1-2 drinks per occasion with 53.2% of men and 71.8% of women in this category Furthermore, 32.5% men and 24.2% women had 3-4 drinks per occasion, while 13.3% men and 4.1% of women indicated consuming ≥5 drinks per occasion.

The types of alcohol were categorized into never, light, moderate, and heavy consumption for beer, wine, and spirits. Among all participants, 13.3% of men and 48.3% of women who never consumed beer. Light beer consumption was noted in 2.5% of men and 7.2% of women, while moderate to heavy beer consumption was observed in men 6.0% and 78.2%, as well as 9.7% and 34.9% for women, respectively. Notably, 571% of men and 63.0% of women were measured with heavy alcohol consumption. In terms of spirits, light consumption was recorded at 49.4% for men and 20.7% for women

Table 3: Alcohol Consumption Categorized by Drinking Patterns and Types of Alcohol in Men and Women.

Alcohol variables						
Variables	**Total**		**Men**		**WOMEN**	
	N 17243	%	N 8280	% 48.0	N 8963	% 52.0
Alcohol frequency						
• Never • Light • Moderate • Heavy	63 11547 4543 1090	0.4 67.0 26.3 6.3	16 5278 2372 614	0.2 63.7 28.6 7.4	47 6269 2171 476	0.5 69.9 24.2 5.3
Drinks per occasion						
• 1-2 drinks • 3-4 drinks • ≥5 drinks	10837 4854 1552	62.8 28.2 9.0	4405 2689 1186	53.2 32.5 14.3	6432 2165 366	71.8 24.2 4.1

Alcohol Types						
1. Beer						
• Never • Light • Moderate • Heavy	5427 852 1365 9599	31.5 4.9 7.9 55.7	1009 211 495 6475	13.3 2.5 6.0 78.2	4328 641 870 3124	48.3 7.2 9.7 34.9
2. Wine						
• Never • Light • Moderate • Heavy	2896 1886 2085 10376	16.8 10.9 12.1 60.2	1618 933 1004 4725	19.5 11.3 12.1 57.1	1278 953 1081 5651	14.3 10.6 12.1 63.0
3. Spirits						
• Never • Light • Moderate to heavy	10537 5949 757	61.1 34.5 4.4	3523 4091 666	42.5 49.4 8.0	7014 1858 91	78.3 20.7 1.0

Note: Alcohol frequency, drinks per occasion and types of alcohol, presented as proportions (%).

3.2 Cox Regression Analysis for Study Population

3.2.1 Association between Alcohol Frequency and AF

In comparison with light drinker, men who never consumed alcohol had a HR of 3.90 (95% CI: 0.97-15.74), suggesting that they face nearly four times the risk of developing AF, although this finding was not statistically significant (Table 4). Men consuming moderate alcohol, HR 1.28 (95%CI :1.01-1.64) and heavy alcohol consumption with a HR of 1.84 (95%CI:1.29-2.91), was associated with higher risk of AF, respectively and these association were statistically significant. In the adjusted models, no associations were found for never, moderate, and heavy alcohol consumption.

In crude analyses, women who never consumed alcohol had a HR of 5.05 (95%CI: 1.86-13.71) indicating that that they have five times the risk of AF compared to light drinker women. Women with a moderate alcohol consumption had no association but women with heavy drinking have a higher risk of AF with HR 1.78 (95%CI:1.04-3.06) indicated significant association. However, in adjusted models, no associations were found for alcohol frequency among women (Table 4).

Table 4: HRs and 95% CIs for the association between Alcohol Frequency and AF in Men and Women.

Variables		Men			Women		
		Crude[1] HR (95%CI)	**Adjusted[2] (Age) HR (95%CI)**	**Adjusted[3] (Age + Confounders) HR (95%CI)**	**Crude[1] HR (95%CI)**	**Adjusted[2] (Age) HR (95%CI)**	**Adjusted[3] (Age+ Confounders) HR (95%CI)**
Alcohol Frequency	**Light**	**Reference**					
	Never	3.90 (0.97-15.74)	2.76 (0.68-11.14)	2.72 (0.66-11.14)	5.05 (1.86-13.71)	2.38 (0.87-6.49)	2.33 (0.84-6.39)
	Moderate	1.28 (1.01-1.64)	1.24 (0.97-1.58)	1.26 (0.98-1.63)	0.98 (0.67-1.41)	0.99 (0.68-1.43)	1.01 (0.69-1.47)
	Heavy	1.84 (1.29-2.61)	1.41 (0.99-2.01)	1.35 (0.94-1.95)	1.78 (1.04-3.06)	1.24 (0.72-2.12)	1.27 (0.72-2.24)

[1]Crude model, [2]Adjusted for age, [3]Adjusted for age and potential confounders. Association of alcohol consumption (g/day) and AF by alcohol frequency. Results from sex-stratified Cox regression models presented with HRs and 95% CIs.

3.2.2 Association between Drinks per Occasion and AF

In men, a consumption of 3-4 drinks per occasion with a HR of 1.01 (95% CI: 0.80-1.29), showed no association compared to reference group (Table 5). However, after adjusting for age, the HR increased to 1.31 (95%CI: 1.02-1.66), suggesting statistically significant high risk of developing AF associated with consuming 3-4 drinks per occasion in men. Further adjusted for age and potential confounders, the HR of 1.30 (95%CI: 1.02-1.67), reinforces the association in men consuming 3-4 drinks per occasion, have a significantly high risk of developing AF independently. Men who consume ≥5 drinks of alcohol, HR is 0.68 (95%CI: 0.47-0.99) was associated with less risk of AF which is statistically significant. There was no association with increased risk with age and further adjusted with age and potential confounders in men consuming ≥5 drinks per occasion.

Women consuming 3-4 drinks and >5 drinks per occasion with HR of 0.41 (95%CI: 0.25-0.12) and HR 0.12 (95%CI: 0.17-0.87) respectively, suggested lower risk of developing AF, a statistically significant reduction indicated moderate and heavy alcohol consumption may be protective against AF in women. Women consumed 3-4 drinks and ≥5 drinks per occasion, in age-adjusted and age with potential confounder adjusted models, no significant associations are present (Table 5).

Table 5: HRs and 95% CIs for the association between Drinks per Occasion and the risk of AF in Men and Women

Variables		Men			Women		
		Crude[1] HR (95%CI)	**Adjusted[2] (Age) HR (95%CI)**	**Adjusted[3] (Age + Confounder) HR (95%CI)**	**Crude[1] HR (95%CI)**	**Adjusted[2] (Age) HR (95%CI)**	**Adjusted[3] (Age + Confounders) HR (95%CI)**
Drinks per Occasion	**1-2 drinks**	Reference					
	3-4 drinks	1.01 (0.80-1.29)	1.31 (1.02-1.66)	1.30 (1.02-1.67)	0.41 (0.25-0.65)	0.73 (0.45-1.18)	0.76 (0.46-1.23)
	≥5 drinks	0.68 (0.47-0.99)	1.28 (0.87-1.88)	1.27 (0.85-1.89)	0.12 (0.17-0.87)	0.44 (0.06-3.22)	0.41 (0.05-3.03)

[1]Crude model, [2]Adjusted for age, [3]Adjusted for age and potential confounders. Association of alcohol consumption and AF by drinks per occasion. Results from sex-stratified Cox regression models presented with HRs and 95% CIs.

3.2.3 Association between Types of Alcohol and AF

The light, moderate, and heavy beer consumption showed no association with risk of AF in crude and adjusted models for both men and women (Table 6). When comparing wine consumption, men who consumed light and heavy wine did not exhibit any association with AF risk. However, moderate wine consumption, associated with an increased AF risk, with a HR 1.56 (95%CI: 1.04-2.33), indicating a significant association. When adjusted for age, the association remained significant, with a HR 1.66 (95%CI: 1.11-2.48). In additions, when further adjusted for age and potential confounders, moderate wine consumption indicated a HR 1.63 (95% CI: 1.08-2.44), reinforcing the significant association between consumption of wine and risk of AF. For women, who consumed light, moderate and heavy wine, no association found with risk of AF. For men, light spirit consumption was associated to a statistically significant high risk of AF with HR of 1.40 (95%CI: 1.10-1.78). However, moderate to heavy spirit consumption did not demonstrate any association with AF risk in either crude or adjusted models. Moreover, women showed no association between spirit consumption (light and moderate to heavy) and AF risk in both crude and adjusted models (Table 6).

Table 6: HR and 95% CIs for the association between Alcohol types and the risk of AF in Men and Women.

Alcohol Types		Men				Women			
		Crude[1] HR (95%CI)	**Adjusted[2] (Age) HR (95%CI)**	**Adjusted[3] (Age + Confounders) HR (95%CI)**	**Total alcohol Adjusted[4] (Age + Confounders) HR (95%CI)**	**Crude[1] HR (95%CI)**	**Adjusted[2] (Age) HR (95%CI)**	**Adjusted[3] (Age + Confounders) HR (95%CI)**	**Total alcohol Adjusted[4] (Age + Confounders) HR (95%CI)**
Beer	Never		Reference						
	Light	1.00 (0.50-1.97)	0.83 (0.42-1.65)	0.82 (0.41-1.61)	0.79 (0.39-1.59)	0.74 (0.39-1.37)	0.71 (0.38-1.33)	0.73 (0.39-1.37)	0.73 (0.38-1.37)
	Moderate	0.99 (0.61-1.60)	1.06 (0.65-1.72)	1.08 (0.66-1.76)	0.99 (0.59-1.66)	0.75 (0.43-1.29)	0.83 (0.48-1.43)	0.79 (0.46-1.38)	0.79 (0.45-1.39)
	Heavy	0.74 (0.54-1.00)	1.02 (0.75-1.39)	1.06 (0.78-1.44)	0.94 (0.66-1.35)	0.57 (0.39-0.82)	0.84 (0.58-1.22)	0.86 (0.59-1.25)	0.86 (0.58-1.27)
Wine	Never		Reference						
	Light	1.18 (0.76-1.84)	1.31 (0.84-2.04)	1.33 (0.85-2.08)	1.43 (0.88-2.31)	0.77 (0.43-1.38)	0.89 (0.49-1.60)	0.89 (0.49-1.60)	0.78 (0.42-1.47)
	Moderate	1.56 (1.04-2.33)	1.66 (1.11-2.48)	1.63 (1.08-2.44)	1.72 (1.10-2.69)	0.77 (0.44-1.35)	0.93 (0.53-1.64)	1.02 (0.58-1.79)	0.91 (0.49-1.67)

	Heavy	1.36 (0.99-1.87)	1.33 (0.96-1.82)	1.35 (0.97-1.88)	1.42 (0.97-2.08)	0.68 (0.45-1.03)	0.76 (0.50-1.15)	0.78 (0.51-1.20)	0.70 (0.43-1.14)
Spirit	Never		Reference						
	Light	1.40 (1.10-1.78)	1.21 (0.95-1.54)	1.24 (0.97-1.57)	1.23 (0.95-1.59)	1.18 (0.82-1.69)	0.98 (0.68-1.40)	0.96 (0.67-1.39)	1.02 (0.70-1.49)
	Moderate to heavy	1.48 (0.99-2.21)	1.22 (0.82-1.82)	1.19 (0.79-1.78)	1.19 (0.78-1.80)	1.92 (0.61-6.05)	1.63 (0.51-5.13)	1.80 (0.57-5.71)	1.96 (0.61-6.28)

[1]Crude model, [2]Adjusted for age, [3]Adjusted for age and potential confounders, [4]Adjusted with age, potential confounders with total alcohol consumption (g/day). Association of alcohol consumption and AF by types of alcohol. Results from sex-stratified Cox regression models presented with HRs and 95% CIs.

In addition, total alcohol consumption (g/day) was analyzed with alcohol types, adjusted with age and potential confounders. The findings from Cox regression analysis indicated similar HRs of wine, beer and spirit (Table 6). Interaction analysis indicated the following *p*-values between sex and alcohol variables: such as alcohol frequency ($p<0.646$), drinks per occasion ($p<0.001$), and types of alcohols such as beer ($p<0.696$), wine ($p<0.06$) and spirits ($p<0.65$) in relation to AF. The *p*-value to show interaction between sex and total alcohol consumption was $p>0.02$.

CHAPTER 4

DISCUSSION

4.1 Scientific Discussion

The present study indicates a statistically significant association between alcohol consumption and incidence of AF across drinking patterns (alcohol frequency and drinks per occasion) and types of alcohol, particularly among men as compared to women. Notably, the study findings indicated that men exhibited an increased risk of AF in association with moderate and heavy alcohol consumption, while women did not exhibit a similar risk and might even experience a protective effect from alcohol. Specifically, consumption of light spirit was significantly associated to an increased risk of AF among men.

This finding aligns with previous meta-analysis, suggesting that even light consumption of alcohol may increase the AF risk [41]. Interestingly, the study also found that moderate wine consumption was associated with an increased AF risk, further adjustment for age and potential confounders, the alcohol consumption shows stronger association risk of AF incidence, which increases independently.

The study findings indicated that the quantity of alcohol consumed, drinking patterns, and alcohol type have been related to the higher risk of AF incidence [16], and our findings shoe consistency with several previous studies such as Johansson et al. highlighted that alcohol consumption was associated with higher risk of AF in men when compared to women [38] and the results of another study by Gallagher et al. reported that moderate alcohol consumption increased the risk of AF significantly in men but not in women [37].

Another meta-analysis conducted by Zhang et al. reported that moderate as well as heavy alcohol consumption was significantly associated to AF risk in men, while in women this association was primarily observed with heavy alcohol consumption [29], also support our results, indicating that women who consumed heavy alcohol showed 78% increased risk of AF. However, our study results contradict the findings of Csengeri et al., who reported that low doses of all types of alcohol were associated to an increased risk of AF [16].

Different studies have presented varying outcomes (inconsistencies) regarding the impact of specific types of alcohol on AF risk: Yang et al. suggested that the alcohol types did not significantly affect AF risk [50], while a prospective study noted that beer and spirit had detrimental effect on AF risk, but wine consumption appeared to have no harmful effects [36]. Another prospective study by Larsson et al, found that beer, wine, and spirit were associated with higher risk of AF at different consumption levels (7-14 and >14 units of alcohol/week) [19, 40].

Despite the evidence that women typically consume less alcohol than men [19], some studies reported that no significant sex-differences were present in association between alcohol consumption and risk of AF. This is contrary to our findings, which demonstrated a strong association between alcohol consumption and increased AF risk specifically among men. However, men were more predisposed to alcohol related high risk of AF [51], evident from a meta-analysis that men were more susceptible to develop alcohol related AF as compared to women [50]. Many studies have not demonstrated an increased risk of AF in women at any level of alcohol consumption, often due to a limited number of women participants consuming heavy alcohol [19].

In our study, a smaller number of women reported heavy drinking, which may have influenced the results. Additionally, one sex-specific prospective study that included nearly equal numbers of men and women did not find significant sex differences in the relationship between alcohol consumption and risk of AF. This opposes our findings, which showed a robust association in men but not in women [36]. A population-based cohort study described that both moderate alcohol consumption and heavy alcohol consumption showed association with AF in both sexes but highlighted that heavy drinking (specifically 35 drinks per week), associated with a stronger AF risk only in men [52], does not align with our data regarding women.

4.2 Biological and Pathophysiological Mechanisms

For the incidence and development of AF, several pathogenic mechanisms in alcohol consumers have been identified [34]. In the genesis of AF, various pathophysiological factors have been considered such as hemodynamic (increase in intra atrial pressure), electrophysiological (shortened refractory period, ionic channels and genetics), structural (atrial fibrosis and inflammation), autonomic (modulatory changes) and atrial tachycardias (triggering factors). Although, alterations in pathophysiological mechanism lead towards fibrillation and

changes in atrial structure with an interruption in electrical activity (disorganized) [14]. Alcohol consumption (acute or chronic) have direct effect on the heart by causing multiple disorders in the electrophysiology, alter functions of ion channel, resulted into disrupted electrical conduction with increased arrhythmias susceptibility [19]. In addition, structural remodelling of left atria lead to hypertension, is another potential pathophysiological mechanism for onset of alcohol related AF, resulted into direct toxic effect of alcohol consumption on heart and considered independent risk factor for AF [33, 34].

4.3 Methodological Discussion

Tromsø Study is a comprehensive, longitudinal cohort research study based on population, conducted in the Tromsø municipality of Norway [43], comprising seven surveys conducted from 1974 to 2016 [45]. Its primary aim is to address the high mortality rates associated with cardiovascular diseases in Norway and followed a defined population over time to assess various health outcomes [43].The participants must have attended at least one of the seven surveys [45]. Tromsø7 facilitated the investigation of the AF incidence and its association with alcohol consumption within a defined population. The data utilized in this study is linked to several registries, including the National Causes of Death Registry, the discharge diagnosis registry at UNN, and the Population Register of Norway. This design allowed to follow the participants until either date of their first recorded AF diagnosis, or the end of follow-up period (31-12-2021) [47, 49].

4.3.1 Internal validity

Internal validity defined as the extent to which the results of a study are reliable and valid to the population under investigation. It can be affected by the two main factors, bias and confounding. Bias is the systematic error that can occur at any stage of the study and may distort the true association in any direction. Bias has been categorized as selection bias and information bias. While it is impossible to eliminate bias completely from a study, it can be minimized through careful planning and analysis to enhance internal validity [53].

4.3.1.1 Selection Bias

A systematic error that occurs in a study when participants are not representative of the general population, from which the samples are drawn, known as selection bias [53, 54]. This type of

bias can be reduced by maintaining a high attendance rate. In the Tromsø7 the attendance rate was 64.7%, indicating that the participants were representative (of the general population), which enhances the internal validity of the study.. However, the 35.3% of participants who did not attend Tromsø7 may introduce non-response bias (a form of selection bias) since they could be systematically different from those who did attend. Attendees may differ from non-attendees in terms of lifestyle, health, and demographic characteristics [55]. Therefore, individuals who consume heavy alcohol may have higher risk of illness and could be less likely to participate, which is an important consideration [56]. Moreover, participants with missing data on alcohol consumption and other covariates have been excluded from the analysis.

4.3.1.2 Information Bias

An information bias may occur during data collection, representing inadequate information about the study participants. One of the most significant forms of information bias is misclassification, which occurs when there is biased detection of exposure or outcome assessments. Misclassification can be categorized as either differential, where the misclassification of participants differs between study groups, or non-differential, where the misclassification of participants is consistent across all groups [53]In this study, misclassification of AF presents a potential bias. Although AF cases were identified through linkage to the UNN, there are still individuals who may be unaware that they have AF. Furthermore, both differential (where one group may have has more difficulty recalling their history than another) and non-differential (where all participants fail to remember the event) [53] misclassification issues may arise. Data on alcohol consumption and other variables were gathered through self-reported questionnaires, such as Q1 [45] with any self-assessment tool, which can introduce recall bias and measurement errors. Utilizing an online questionnaire could enhance data quality by minimizing administrative burdens and the likelihood of misclassification [45]. Self-reported lifestyles, in various studies used as covariates were susceptible to measurement error that can lead to information bias. Participants often overreport the positive qualities such as physical activity in leisure time, while understate the negative behaviours (such as smoking and alcohol consumption) [57]. Although, the information regarding BMI, hypertension or use of antihypertensive drugs was collected through physical examinations and self-reported measures, this still contributed to the misclassification of participants in the study.

Nevertheless, validation studies indicate that variables are self-reported were considered accurate [55]. Furthermore, the self-reported education levels in the Tromsø7 are validated and confirmed about the data which is suitable for research purposes [58, 59].

4.3.1.3 Confounding

Confounding defined as the influence of an exposure of interest linked to the effect of another variable, which can obscure the true relationship between the exposure and the outcome [53, 54]. For instance, the presence of a confounder may lead to an observed association that differs from the actual association between the exposure and the outcome. Confounding can be controlled/accounted through various statistical approaches such as stratification and multivariable regression analysis. In this study all statistical analyses were sex-stratified and potential confounders including age, smoking status, systolic and diastolic BP, hypertension, education level, physical activity, BP drugs and BMI, were controlled appropriately. However, confounding caused by some unknown factors, such as measurement errors, uncontrolled variables, and interaction defects, remain unaddressed.

4.3.2 External validity

External validity defined to which extent the findings of a study can be applied to different populations [53]. Tromsø7 included participants from municipality of Tromsø, and mainly are of Norwegian origin (85%) [45]. Participants were enrolled based on the official population registry, with invitations sent to the general population. The overall attendance rate was 64.7%. Majority of the study participants belonged to white, European ancestry, also few immigrants from other countries. Therefore, the population represented in the Tromsø Study can be considered comparable to other Caucasian populations regarding the AF incidence with associated risk factors. In addition, the presence of only one hospital in the area facilitated endpoint identification, enhancing the reliability of the data. The study design, high attendance rate for Tromsø7, and the reliability of endpoints contribute to its high external validity and generalizability.

4.4 Strengths and Limitations

The large sample size study from Tromsø7 with high attendance rate of 64.7%, representative of both Tromsø and general population of Norway due to similar demographic

characteristics[55], thereby enhancing the reliability and the validity of the findings, is the key strength of this study. Another strength of Tromsø7 is comprehensive data collection with broad range of information obtained through the questionnaires and physical examination, reduces the chance of confounders being missed, ensures the collection of valid and reliable data. All cases of AF were confirmed and further validated by an independent endpoint committee according to guidelines.

Nonetheless, the study has several limitations. The alcohol consumption was self-reported by the participants, which may cause over/under-estimation of the risk factors for AF due to potential inaccuracies in reporting of alcohol consumption. The complete case analyses were performed to include participants with non-missing data on the variables considered in this study, which resulted to a substantial reduction in the sample size and lower precision of the findings. Moreover, it can introduce bias if the missing data are not missing completely at random [60]. Another limitation is the reduced power to detect differences in women due to wide CIs, even though point estimates were consistent for both men and women. Furthermore, there remains a risk of misclassification of AF, as some patients have silent AF that goes undiagnosed or undetected. Consequently, the actual incidence of AF may be greater than what is represented here. To avoid potential misclassification bias, participants with suspected AF information (data) were excluded from the study.

4.5 Future Implications

The current study has potential to make a valuable contribution by supporting previous research studies that demonstrates an association between alcohol consumption and incidence of AF. These findings may be significant and could prompt further investigations into relationship of alcohol consumption with health-related behaviours, as well as to ascertain the existence of sex disparities identified in this study. It also suggests that risks of AF associated with alcohol consumption, influenced by overall health of individuals, making it crucial to implement future public health interventions aimed at the most vulnerable individuals. Alcohol consumption and AF were found to be more strongly associated, particularly among men, which emphasizes the potential need for sex-specific risk assessments for AF.

A better understanding to acquire a comprehensive insight regarding the impact of alcohol related with risk of AF, health conditions and overall well-being, may effectively contribute to achieving the Sustainable Development Goals both in Norway and globally. Due to variations in drinking patterns and types of alcohol consumed, and the age at which

individuals begin drinking across various cultures, communities, and countries, findings related to alcohol consumption may not always be generalized. Therefore, research conducted on specific population like Tromsø7, can be crucial for understanding the cultural differences to develop and implement interventions to address the needs of specific population groups.

CONCLUSION

In conclusion, this study provides valuable insights into relationship between alcohol consumption and incidence of AF. We found a positive association between alcohol consumption and an increased risk of AF in men; however, no such association was observed in women. Although, our findings demonstrate that alcohol consumption across drinking patterns (alcohol frequency and drinks per occasion) and different alcohol types (wine, and spirit) are strongly associated with increased risk of AF and support existing literature. To comprehend the underlying mechanisms of sex differences, and to explore potential interventions to mitigate alcohol related risk of AF more research studies are recommended.

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Appendix 1: Invitation letter from The Tromsø7 (2015-2016)

Forespørsel om deltakelse i Tromsøundersøkelsen

Hva er Tromsøundersøkelsen?

Tromsøundersøkelsen er en folkehelseundersøkelse. Formålet er å samle inn opplysninger til forskning som gir økt kunnskap om helse og sykdom, og hvordan folkehelsen kan forbedres gjennom forebygging og behandling.

Tromsøundersøkelsen startet i 1974 med bakgrunn i den høye forekomsten av hjerte -og karsykdom i Nord-Norge. Siden den gang er undersøkelsen gjennomført med 6-7 års mellomrom og dette er den sjuende runden.

Ved å delta bidrar du til viktig forskning om forekomst, forebygging og behandling av sykdom, hva som fremmer god helse, og hva som er årsak til helseproblemer.

Ditt bidrag teller!

Hvorfor spør vi deg?

Alle innbyggere i Tromsø kommune fra 40 år og oppover spørres om å delta. I tillegg inviterer vi ca.1000 personer i alderen 21-25 år. Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk.

Sammen med denne informasjonsbrosjyren finner du en invitasjon med praktiske opplysninger om undersøkelsen.

Det er gratis å delta i Tromsøundersøkelsen. Trenger du videre undersøkelse eller oppfølging av fastlegen eller spesialisthelsetjenesten, betaler du vanlig egenandel.

Slik foregår undersøkelsen

Alle deltakere inviteres til en hovedundersøkelse som omfatter spørreskjema, intervju, blodprøver og undersøkelser. Et helt tilfeldig utvalg av deltakere inviteres tilbake til en spesialundersøkelse som omfatter flere prøver og mer omfattende undersøkelser. Alle undersøkelsene gjennomføres av helsepersonell.

Tilbakemelding

Noen uker etter undersøkelsen får du et brev med noen resultater, det vil si høyde, vekt, BMI, hemoglobin, blodtrykk, kolesterolnivå og om du har diabetes. Det gis ikke rutinemessig tilbakemelding om resultater av andre blodprøver eller målinger. Dersom prøveresultatet viser at det er nødvendig med oppfølging av lege eller henvisning til spesialist, vil du få råd om det. Ved behov for henvisning til spesialist, sørger vi for å sende henvisning.

Du kan reservere deg mot å få vite resultatene av prøvene dine. Men hvis et prøveresultat krever rask legebehandling vil du likevel bli kontaktet.

Du vil også få informasjon om undersøkelsen underveis gjennom aviser, sosiale medier (Facebook, Twitter m.m) samt på arrangementer som "Lørdagsuniversitetet" og "Forskningsdagene".

Frivillig deltakelse

Det er frivillig å delta i Tromsøundersøkelsen.
Om du sier ja til å delta, kan du når som helst trekke tilbake samtykket.

Hva omfatter den sjuende Tromsøundersøkelsen?

Hva skal vi forske på?

I denne runden av Tromsøundersøkelsen er det mer enn 50 prosjekter som skal forske på forekomst, forebygging og behandling av folkehelseproblemer.

Det skal blant annet forskes på hjerte- og karsykdommer, kreft, lungesykdommer, aldring og demens, fedme, diabetes, legemiddelbruk, psykisk helse, kronisk smerte, tannhelse, muskel- og skjelettplager, risikofaktorer som alkohol, fysisk aktivitet og kosthold, nyrer og urinveier, hudproblemer, miljøgifter, infeksjoner og antibiotikaresistens, nervesystemet, sosial ulikhet, samspill mellom arv og miljø, søvn og bruk av helsetjenester.

Du finner mer informasjon om forskningen på vår internettside, www.tromsoundersokelsen.no

Spørreskjema

Deltakernes informasjon om egen helse er en svært viktig del av Tromsøundersøkelsen. Vi ber deg derfor fylle ut to spørreskjema. Alle spørsmål kan besvares på nett. Det ene skjemaet er vedlagt i papirform, hvis du foretrekker det. Fyll det gjerne ut før du møter opp så sparer du tid under undersøkelsen. Hvis du trenger assistanse vil personalet hjelpe deg på undersøkelsen hvor det også er satt opp egne datamaskiner til dette.

Utfylte svar i spørreskjema er like viktig for forskningen som resultater fra blodprøver og kliniske undersøkelser.

Du kan delta på Tromsøundersøkelsen selv om du ikke ønsker å være med på alle deler av undersøkelsen.

Hovedundersøkelsen

Helsepersonell veileder deg gjennom undersøkelsen som varer ca. en time hvis du har fylt ut spørreskjemaene på forhånd. Du får også time til spesialundersøkelsen hvis du er valgt ut til denne.

Vi starter med noen enkle spørsmål knyttet til undersøkelsene du skal gjennomføre. Videre måler vi høyde, vekt, hofte- og livvidde, blodtrykk og puls.

Det tas deretter prøver og gjøres noen kliniske undersøkelser:

Blodprøve. Det tas blodprøver til bruk for forskning som samlet er mye mindre enn det en blodgiver gir. Det fryses ned prøver til bruk for senere analyser og forskning. Arvestoff (DNA/RNA) vil bli lagret til bruk for forskning.

Bakterieprøve fra nese og hals for å se etter gule stafylokokker, en bakterie som normalt finnes på hud og slimhinner hos mennesker, men som i enkelte tilfeller kan forårsake alvorlige infeksjoner. Prøvene tas med en fuktet vattpensel.

Spyttprøver til bruk for forskning knyttet til tannhelse, virusinfeksjon og kreft.

Smertefølsomhet måles med to metoder. Først holder du hånden i kaldt vann i opptil 90 sekunder,deretter får du en blodtrykksmansjett plassert rundt leggen som blåses opp. Underveis angir du hvor mye smerte du opplever, og kan avbryte testene når som helst hvis det blir for ubehagelig.

Tannsjekk som omfatter et røntgenbilde av kjeven, registrering av hull i tennene og betennelsessykdom i tannkjøttet.

Fysisk aktivitet og kosthold. Utvalgte deltakere blir bedt om å registrere fysisk aktivitet ved bruk av aktivitetsmåler og registrering av kosthold i en periode.

Du får også utdelt utstyr for innlevering av urin- og avføringsprøve hvis du er valgt ut til spesialundersøkelsen.

Spesialundersøkelsen

Et tilfeldig utvalg av deltakere inviteres til spesialundersøkelsen som gjennomføres noen uker etter hovedundersøkelsen. Denne varer totalt ca. 2 timer, avhengig av hvor mange deler du blir spurt om å være med på.

Ved oppmøte vil urinprøvene samles inn, og det tas noen nye blodprøver. Deler av blodprøvene fryses ned for senere forskning beskrevet i denne brosjyren.

Videre inviteres du til én eller flere av disse undersøkelsene:

EKG er en registrering av hjerterytmen som også kan gi informasjon om hjertesykdom. Ved registrering festes ledninger til kroppen.

Kognitiv funksjon testes ved hjelp av enkle spørsmål knyttet til gjenkjenning av ord, kopling av symboler og tall samt grad av fingerbevegelighet.

Fysisk funksjon undersøkes ved å teste balanse, gange og gripestyrke.

Ultralyd av halspulsåre gjøres for å se etter forkalkninger og innsnevringer av årene. Undersøkelsen kartlegger også blodforsyningen til hjernen.

Fotografering av øyebunnen gir bilder som både sier noe om synet og om tilstanden til blodkarene i kroppen. Det gis en øyendråpe i hvert øye en tid før fotografering for at pupillene skal utvide seg. Dette kan svi noe og synet kan forbigående bli noe uklart. Effekten går gradvis over, og er borte etter en time. I tillegg gjøres det en enkel synstest som du får svar på umiddelbart.

Lungefunksjonen testes ved at du puster så hardt du klarer gjennom et munnstykke. Hvor mye luft som blåses ut pr. sekund, er et mål på lungefunksjonen din. I tillegg vil det gjøres lydopptak av lungelyder og hjertelyder.

Måling av beintetthet. Ved hjelp av ultralyd foretas det beintetthetsmåling som brukes til å undersøke risiko for beinskjørhet og brudd.

Ultralyd av hjertet gjøres for å undersøke hjertets form og funksjon.

Videre bruk av opplysninger og prøver i forskning

Personvern

All informasjon du gir til Tromsøundersøkelsen behandles med respekt for personvern og privatliv, og i samsvar med lover og forskrifter.
Alle medarbeidere som jobber med undersøkelsen har taushetsplikt. Opplysningene som samles inn skal bare brukes til godkjente forskningsformål. Det vil ikke være mulig å identifisere deg når resultatene av forskningen publiseres.

UiT Norges arktiske universitet ved universitetsdirektøren er ansvarlig for behandlingen av personopplysninger. Tromsøundersøkelsen har konsesjon fra Datatilsynet. Regional komité for medisinsk og helsefaglig forskningsetikk i Nord-Norge (REK nord) har gjort en etisk og helsefaglig vurdering av undersøkelsene som gjennomføres, samt godkjent innsamlingen av prøver.

Hvilke data lagres i Tromsøundersøkelsen?

I Tromsøundersøkelsen lagres opplysninger gitt av deltakere i de forskjellige rundene av Tromsøundersøkelsen. Det lagres også opplysninger om kreftdiagnoser og dødsårsaker fra Kreftregisteret og Dødsårsaksregisteret.
For deltakere som har eller får diagnoser innen hjerte- og karsykdom, diabetes og beinbrudd, innhentes opplysninger fra sykejournalen i spesialist- og primærhelsetjenesten som er nødvendig for å kvalitetssikre aktuelle diagnoser. Dette for å sikre forskning av høy kvalitet. Tilsvarende vil også kunne bli aktuelt for andre sykdommer det forskes på i Tromsøundersøkelsen.

Hvordan lagres dine opplysninger og prøver?

Alle opplysningene og prøvene lagres uten navn og fødselsnummer.

En kode knytter deg til dine opplysninger og prøver. Det er kun noen få autoriserte personer som kan finne tilbake til deg gjennom en egen kodenøkkel.

De biologiske prøvene lagres i godkjent forskningsbiobank ved Institutt for samfunnsmedisin, UiT. Leder av Tromsøundersøkelsen er ansvarlig for biobanken. Den er registrert i Folkehelseinstituttets Biobankregister (nr 2397). Det biologiske materialet kan bare brukes etter godkjenning fra REK.

Utlevering av opplysninger og prøver til forskere

Hvis du sier ja til å delta i studien, samtykker du til at dine opplysninger og prøver kan brukes videre i forskning på ubestemt tid. Medisinsk forskning forandrer seg hele tiden, og i fremtiden kan data bli brukt i forskningsprosjekter forutsatt at det er i samsvar med gjeldende lover og forskrifter.

Alle forskningsprosjekter som får data fra Tromsøundersøkelsen må være i samsvar med lover og forskrifter. Prosjektleder må tilhøre en kompetent forskningsinstitusjon. Den enkelte forsker vil kun få tilgang til personidentifiserende opplysninger etter å ha innhentet nødvendige godkjenninger fra REK, og/eller Datatilsynet.

I noen forskningsprosjekter kan prøver og avidentifiserte opplysninger bli utlevert til andre land. Det vil skje i en slik form at våre utenlandske samarbeidspartnere ikke kan knytte prøvene opp mot deg som person.

I noen prosjekter kan det bli aktuelt å kontakte deg igjen for å samle inn flere data, f.eks. ved spørreskjema, intervju eller kliniske undersøkelser. Du vil da få ny informasjon og bes om nytt samtykke til det konkrete prosjektet.

Ved å delta i Tromsøundersøkelsen bidrar du til viktig forskning på sykdom og helse, oppbygging av fagmiljøer og bedre pasientbehandling.

Sammenstilling med andre registre

I noen forskningsprosjekter vil opplysninger om deg kunne bli sammenstilt med:

Opplysninger du har gitt i tidligere runder av Tromsøundersøkelsen hvis du har deltatt i Tromsøundersøkelsen før.

Opplysninger fra barn, søsken, foreldre og besteforeldre som har deltatt i Tromsøundersøkelsen.

Opplysninger om deg i nasjonale helseregistre som Reseptregisteret, Medisinsk fødselsregister, Kreftregisteret, Norsk pasientregister, Hjerte- og karregisteret, Dødsårsaksregisteret, infeksjonsregistre og andre nasjonale sykdoms- og kvalitetsregistre.

Helseopplysninger om deg fra primær- og spesialisthelsetjenesten.

Opplysninger om sosiale forhold som arbeid, utdanning, inntekt, boforhold osv. fra registre hos bl.a. Statistisk sentralbyrå og NAV.

Slike sammenstillinger krever som regel forhåndsgodkjenning av offentlige instanser, som REK og/eller Datatilsynet.

Rett til innsyn og sletting av dine opplysninger og prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har også rett til å få korrigert eventuelle feil i opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller er brukt i vitenskapelige artikler.

Finansiering

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Forsikring

Deltakere i Tromsøundersøkelsen er forsikret gjennom Norsk Pasientskadeerstatning.

Samtykke til deltakelse i studien

Hvis du vil delta i den sjuende Tromsøundersøkelsen, må du gi skriftlig samtykke ved oppmøte. Personalet vil gi mer informasjon og svare deg dersom du har spørsmål i forbindelse med samtykket.

Du kan når som helst trekke tilbake samtykket ditt.


Dine svar bidrar til bedre folkehelse for våre kommende generasjoner
Her finner du oss:
Heiloveien 6 (tidligere Langnes legesenter)
9015 Tromsø
Telefon 77 62 07 00
Epost tromso7@uit.no
Nettside www.tromsoundersokelsen.no
Tromsø-undersøkelsen
UNIVERSITETET I TROMSØ

Appendix 2: Questionnaire 1 from the Tromsø7 (2015-2016)

The Tromsø Study
2015–2016

CONFIDENTIAL

The questionnaire will be optically read. Please, use blue or black inked pen only. Use block lettering. Refrain from the use of comma.

Date for filling in the questionnaire: ☐☐☐☐☐☐

HEALTH AND DISEASES

1.1 How do you in general consider your health to be?

Excellent	Good	Neither good nor bad	Bad	Very bad
☐	☐	☐	☐	☐

1.2 How is your health now compared to others of your age?

Excellent	Good	Neither good nor bad	Bad	Very bad
☐	☐	☐	☐	☐

1.3 Have you ever had, or do you have?
Tick once for each line.

	No	Yes, currently	Previously, not now	Age first time
High blood pressure	☐	☐	☐	☐☐
Heart attack	☐		☐	☐☐
Heart failure	☐	☐	☐	☐☐
Atrial fibrillation	☐	☐	☐	☐☐
Angina pectoris *(heart cramp)*	☐	☐	☐	☐☐
Cerebral stroke / brain haemorrhage	☐		☐	☐☐
Diabetes	☐	☐	☐	☐☐
Kidney disease, not including urinary tract infection *(UTI)*	☐	☐	☐	☐☐
Bronchitis / emphysema / COPD	☐	☐	☐	☐☐
Asthma	☐	☐	☐	☐☐
Cancer	☐	☐	☐	☐☐
Rheumatoid Arthritis	☐	☐	☐	☐☐
Arthrosis	☐	☐	☐	☐☐
Migraine	☐	☐	☐	☐☐
Psychological problems for which you have sought help	☐	☐	☐	☐☐

1.4 Do you have persistent or constantly recurring pain that has lasted for three months or more?

☐ No ☐ Yes

DENTAL HEALTH

2.1 How do you consider your own dental health to be?

Very bad	1	2	3	4	5	Excellent
	☐	☐	☐	☐	☐	

2.2 How satisfied or dissatisfied are you with your teeth or denture?

Very dissatisfied	1	2	3	4	5	Very satisfied
	☐	☐	☐	☐	☐	

USE OF HEALTH SERVICES

3.1 Have you during the past 12 months visited?

	Yes	No	Number of times
General practitioner *(GP)*	☐	☐	☐☐
Emergency room	☐	☐	☐☐
Psychiatrist / Psychologist	☐	☐	☐☐
Another medical specialist than a general practitioner *(GP)* or a psychologist or psychiatrist *(not at a hospital)*	☐	☐	☐☐
Dentist / dental services	☐	☐	☐☐
Pharmacy *(to buy / get advice about medicines / treatment)*	☐	☐	☐☐
Physiotherapist	☐	☐	☐☐
Chiropractor	☐	☐	☐☐
Acupuncturist	☐	☐	☐☐
CAM provider *(homeopath, reflexologist, spiritual healer etc.)*	☐	☐	☐☐
Traditional healer *(helper, "reader" etc.)*	☐	☐	☐☐
Have you during the past 12 months communicated with any of the services above by using the Internet?	☐	☐	☐☐

3.2 Have you over the past 12 months visited a hospital?

	Yes	No	Number of times
Hospital admission	☐	☐	☐☐
Visited an out-patient clinic:			
Psychiatric out-patient clinic	☐	☐	☐☐
Other out-patient clinics (not psychiatric department)	☐	☐	☐☐

USE OF MEDICIN

4.1 **Do you use or have you used?** *Tick once for each line.*

	Never	Now	Previously, not now	Age first time
Blood pressure lowering drugs	☐	☐	☐	
Cholesterol lowering drugs	☐	☐	☐	
Diuretics	☐	☐	☐	
Drugs for heart disease *(for example anticoagulants, antiarrhythmics, nitroglycerin)?*	☐	☐	☐	
Insulin	☐	☐	☐	
Tablets for diabetes	☐	☐	☐	
Drugs for hypothyroidism (Levaxin or thyroxine)?	☐	☐	☐	

4.2 **How often during the past four weeks have you used?** *Tick once for each line.*

	Not used in the past 4 weeks	Less than every week	Every week but not daily	Daily
Painkillers on prescription	☐	☐	☐	☐
Painkiller non-prescription	☐	☐	☐	☐
Acid suppressive medication	☐	☐	☐	☐
Sleeping pills	☐	☐	☐	☐
Tranquillizers	☐	☐	☐	☐
Antidepressants	☐	☐	☐	☐

4.3 **State the name of all medicines, both those on prescription and non-prescription drugs, you have used regularly during the last 4 weeks.** *Do not include nonprescription vitamin-, mineral- and food supplements, herbs, naturopathic remedies etc.*

If there is not enough space for all medicines, continue on a separate sheet.

DIET

5.1 **Do you usually eat breakfast every day?**

☐ No ☐ Yes

5.2 **How many units of fruit or vegetables do you eat on average per day?** *One unit is by example one apple, one salad bowl.*

Number of units

5.3 **How often do you eat these food items?** *Tick once for each line.*

	0–1 times per month	2–3 times per month	1–3 times per week	4–6 times per week	Once a day or more
Red meat *(All products from beef, mutton, pork)?*	☐	☐	☐	☐	☐
Fruits, vegetables, and berries?	☐	☐	☐	☐	☐
Lean fish *(Cod, Saithe)?*	☐	☐	☐	☐	☐
Fat fish *(salmon, trout, redfish, mackerel, herring, halibut)?*	☐	☐	☐	☐	☐

5.4 **How many glasses / containers of the following do you normally drink / eat?** *Tick once for each line.*

	Rarely / never	1–6 glasses per week	1 glass per day	2–3 glass per day	4 or more per day
Milk / Yogurt with probiotics (Biola, Cultura, Activia, Actimel, BioQ etc.)	☐	☐	☐	☐	☐
Fruit juice	☐	☐	☐	☐	☐
Soft drinks with sugar	☐	☐	☐	☐	☐
Soft drinks with artificial sweeteners	☐	☐	☐	☐	☐

5.5 **How many cups of coffee or tea do you usually drink daily?** *Put 0 for the types you do not drink daily.*

	Number of cups
Filtered coffee	
Boiled coffee / french plunger coffee *(coarsely ground coffee for brewing)*	
Instant coffee	
Cups of espresso-based coffee *(from coffee-machines, capsules etc.)*	
Black tea *(e.g. Earl Grey, Black currant)*	
Green tea / white tea / oolong tea	
Herbal tea *(e.g. rose hip tea, chamomile tea, Rooibos tea)*	

HEALTH ANXIETY

	Not at all	A little bit	Moderately	Quite a bit	A great deal
6.1 **Do you think there is something seriously wrong with your body?**	☐	☐	☐	☐	☐
6.2 **Do you worry a lot about your health?**	☐	☐	☐	☐	☐
6.3 **Is it hard for you to believe the doctor when he/she tells you there is nothing to worry about?**	☐	☐	☐	☐	☐
6.4 **Do you often worry about the possibility that you have a serious illness?**	☐	☐	☐	☐	☐
6.5 **If a disease is brought to your attention (e.g., on TV, radio, the internet, the newspapers, or by someone you know), do you worry about getting it yourself?**	☐	☐	☐	☐	☐
6.6 **Do you find that you are bothered by many different symptoms?**	☐	☐	☐	☐	☐
6.7 **Do you have recurring thoughts about having a disease that is difficult to be rid ofom?**	☐	☐	☐	☐	☐

PHYSICAL ACTIVITY

7.1 **If you are in paid or unpaid work, which statement describes your work best?** *Tick the most apprioate box.*

- ☐ Mostly sedentary work? *(e.g. office work, mounting))*
- ☐ Work that requires a lot of walking *(e.g. shop assistant, light industrial work, teaching)*
- ☐ Work that requires a lot of walking and lifting *(e.g. nursing, construction)*
- ☐ Heavy manual labour

7.2 **Describe your exercise and physical exertion in leisure time over the last year.** *If your activity varies throughout the year, give an average. Tick the most appropriate box.*

- ☐ Reading, watching TV/screen or other sedentary activity?
- ☐ Walking, cycling, or other forms of exercise at least 4 hours a week? *(including walking or cycling to place of work, Sunday-walking etc.)*
- ☐ Participation in recreational sports, heavy gardening, snow shoveling etc. at least 4 hours a week.
- ☐ Participation in hard training or sports competitions, regularly several times a week?

7.3 **During the last week, how much time did you spend sitting on a typical week or weekend day?** *E.g., at a desk, while visiting friends, while watching TV/screen.*

- ☐☐ Hours sitting on a weekday (both work and leisure hours)
- ☐☐ Hours on a weekend day

ALCOHOL

8.1 **How often do you drink alcohol??**

- ☐ Never
- ☐ Monthly or less frequently
- ☐ 2–4 times a month
- ☐ 2–3 times a week
- ☐ 4 or more times a week

8.2 **How many units of alcohol (1 beer, glass of wine or drink) do you usually drink when you drink alcohol?**

1–2	3–4	5–6	7–9	10 or more
☐	☐	☐	☐	☐

8.3 **How often do you have six or more units of alcohol in one occasion??**

- ☐ Never
- ☐ Less frequent than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

TOBACCO and SNUFF

9.1 **Do you/did you smoke daily?**

☐ Never ☐ Yes, now ☐ Yes, previously

9.2 **Have you used or do you use snuff or chewing tobacco daily?**

☐ Never ☐ Yes, now ☐ Yes, previously

QUESTIONS ABOUT CANCER

10.1 **Have you ever had**

	No	Yes	**If yes:** Age first time	**If yes:** Age last time
A mammogram	☐	☐		
Your PSA (Prostate Specific Antigen) level measured)	☐	☐		
A colon examination (colonoscopy, stool sample test)	☐	☐		

10.2 **Has anyone in your close biological family ever had**

	Children	Mother	Father	Maternal grandmother	Maternal grandfather	Paternal grandmother	Paternal grandfather	Aunt	Uncle	Sibling
Breast cancer	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Prostate cancer	☐		☐		☐		☐		☐	☐
Colon cancer	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

EDUCATION AND INCOME

11.1 **What is the highest levels of education you have completed?** *Tick one box only.*

- ☐ Primary / partly secondary education. *(Up to 10 years of schooling)*
- ☐ Upper secondary education: *(a minimum of 3 years)*
- ☐ Tertiary education, short: College / university less than 4 years
- ☐ Tertiary education, long: College / university 4 years or more

11.2 **What was the household's total taxable income last year?** *Include income from work, social benefits and similar.*

- ☐ Less than 150 000 kr
- ☐ 150 000–250 000 kr
- ☐ 251 000–350 000 kr
- ☐ 351 000–450 000 kr
- ☐ 451 000–550 000 kr
- ☐ 551 000–750 000 kr
- ☐ 751 000 –1 000 000 kr
- ☐ More than 1 000 000 kr

FAMILY AND FRIENDS

12.1 **Who do you live with?**

	Yes	No	Number
Spouse / partner	☐	☐	
Other persons over 18 years	☐	☐	
Persons under 18 years	☐	☐	

12.2 **Do you have enough friends who can give you help and support when you need it?**

☐ Yes ☐ No

12.3 **Do you have enough friends that you can talk confidentially with?**

☐ Yes ☐ No

12.4 **How often do you take part in organised gatherings, e.g., sports clubs, political meetings, religious or other associations?**

Never, or just a few times a year	1–2 times a month	Approximately once a week	More than once a week
☐	☐	☐	☐

WOMAN ONLY

13.1 **How old were you when you first started menstruating?**

Age

13.2 **Are you pregnant at the moment?**

☐ No ☐ Yes ☐ Uncertain

13.3 **How many children have you given birth to?**

Number

13.4 **If you have given birth, how many months did you breast-feed? Fill in for each child the birth year, birth weight and the number of months breast feeding.** *Fill in the best you can*

	Birth year	Birth weight in grams	Months of breastfeeding
Child 1			
Child 2			
Child 3			
Child 4			
Child 5			
Child 6			

MEN ONLY

14.1 **Have you ever had an inflammation of your prostate / urine bladder?**

☐ No ☐ Yes

14.2 **Have you ever had a vasectomy?**

☐ No ☐ Yes **If yes:** Which year was it

Thank you for your contribution.