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Sex-specific association between coffee consumption and inflammation: the population-based Tromsø7 Study.

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Abstract

Introduction: Various studies have explored the association between coffee consumption and the risk of inflammation, yet results are inconsistent. Few studies have examined these association separately in women and men and by type of coffee consumed. We therefore aimed to further investigate this association in a heavy coffee drinking population by including four different methods of coffee brewing and exploring these associations separately for women and men using laboratory measured C-reactive protein (CRP) levels.

Aim: The aim of this study is to examine the association between coffee consumption and inflammation in women and men in the seventh survey of the Tromsø Study (Tromsø7).

Methods and material: This is a cross-sectional study utilizing data from Tromsø7 (2015-2016). After exclusions, the final study sample consisted of 6411 women and 6232 men aged 40 to 100 years. Descriptive statistics were used to describe the study participants according to total coffee consumption, filtered coffee, boiled coffee, instant coffee, and espresso consumption. The differences between the different levels of coffee consumption were tested using Chi-square and ANOVA tests. Odds ratios (ORs) and confidence intervals (CIs) from multivariable binary logistic regression analyses were used to estimate the association between coffee consumption and inflammation. All analyses were performed separately for women and men.

Results: Most women and men consumed high-moderate levels of coffee (3-5 cups per day). The most consumed coffee type was filtered coffee. In women, compared to zero consumers, low moderate, high moderate and heavy consumers had ORs and CIs of 0.73 (0.59-0.90), 0.57 (0.47-0.70), 0.59 (0.47-0.73) respectively. Consumption of filtered coffee, instant coffee, and espresso was associated with a lower risk of inflammation, but no association was found for boiled coffee consumption in women. No associations were found in men.

Conclusion: Coffee consumption is associated with lower risk of inflammation in women but not in men. Further studies are recommended to understand the underlying mechanisms of these sex differences.

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List of abbreviations

BMI	Body Mass Index
CHD	Coronary heart disease
CI	Confidence intervals
CRP	C-reactive protein
DAG	Directed Acyclic Graph
DPU	Data and Publication Committee
EFSA	European Food Safety Authority
FFQ	Food frequency questionnaire
hs-CRP	High-sensitivity CRP
kg/m2	Kilograms per metres squared
mg	Milligrams
mg/dL	Milligrams per 100 millilitres
OR	Odds Ratio
Q1	Questionnaire 1
REK	Regional Committees for Medical and Healthcare Research Ethics
SIKT	The Norwegian Agency for Shared Services in Education and Research
SP2	Singapore Prospective study-2
Tromsø7	The Seventh survey of the Tromsø study 2015-2016
ug/mlL	Microgram per millilitre
UiO	University of Oslo

US	United States
WHO	World Health Organization
24-HR	24-hour recall

1 Introduction

1.1 Inflammation

Inflammation is an adaptive response to harmful stimuli and is commonly triggered by various disease conditions and tissue damage (1, 2). It eliminates infectious agents from the body and supports repair after tissue damage (1, 3, 4). As a defensive response to injury, the resolution of inflammation involves the initiation of endogenous anti-inflammatory mechanisms that protect the body from excessive tissue damage and assist the repair of tissue structure and function (5, 6).

Common causes of inflammation include blood clots, infections, chemical exposure, immune system disorders, physical injury, cancer, and neurological conditions (7-10). In the process of inflammation, the immune system first recognizes a foreign and harmful agent, removes it from the body and then starts the healing process (1, 4, 11-13).

The inflammation process is categorized by five fundamental symptoms. These include redness, heat, swelling, loss of function, and pain (6, 14, 15). Chemical factors that initiate and regulate the inflammatory process are released by damaged tissue, leading to an increase in blood flow, fluids, and immune cells. These in turn cause swelling, heat, and redness (10, 16-18). Pain results from signals from the nervous system and chemical mediators, which in turn lead to loss of function (10, 19, 20).

Various physiological and pathological processes are triggered by inflammation. The pathological features of inflammation are well understood, but its physiological aspects remain unclear (1, 6). Infection and tissue damage are the main instigators of inflammation (1, 2). They lead to the recruitment of inflammatory mediators such as leukocytes and plasma proteins to the inflamed site (1, 11, 21, 22). Inflammatory mediators respond to the inflammation process by releasing substances that mediate the inflammation process to prevent further tissue damage (22).

Inflammation can be categorized as either acute or chronic. Acute inflammation typically resolves within a few hours or days, whereas chronic inflammation can last for an extended period, sometimes even years, following the initial exposure (5, 11, 23, 24). Acute inflammation plays a crucial role in the natural immune system and serves as the first line of defense against foreign substances and harmful molecules (6, 24-26). It is essential for survival during infections and physical injuries (6, 11, 13, 25, 26).

The resolution of acute inflammation is crucial to prevent the progression to chronic inflammation (5, 27). Significant progress has been achieved in recognizing the cellular and molecular mechanisms that occur during the acute inflammatory reaction to infection and tissue damage (1, 28). Although the processes that trigger inflammatory responses are well understood, there is comparatively little information on the resolution of acute inflammation to prevent chronic inflammation (1, 5, 29). To effectively resolve acute inflammation, the harmful stimuli that initiated the process must be neutralized and eliminated to halt the inflammatory response (5, 29, 30). Failure of this process invariably leads to chronic inflammation. The stage between acute and chronic inflammation is referred to as subacute inflammation and can last 2-6 weeks (4). The etiology of the chronic immune response is dictated by the nature of the triggering agent (4, 5, 30).

Inflammation lasting for months and even years is often linked to severe detrimental side effects on health and can result in several diseases that together account for the major causes of global disability and death (6, 11). Chronic inflammation is a crucial factor in many diseases that leads to considerable morbidity and early mortality (4, 11, 31). Conditions linked to chronic inflammation include cardiovascular disease, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease and autoimmune and neurodegenerative disorders (11, 32).

Studies have shown that women and men differ in their responses to inflammation (33-35). The production of immune cells also differs between the sexes (33). Thus. women and men respond differently to inflammatory diseases. According to a study by Di Florio et al., the most distinctive characteristics of autoimmune diseases are due to sex differences in the immune system (36).

Emerging evidence suggests that the risk of developing chronic inflammation may be connected to a person's childhood development, leading to long-lasting impacts on their adult health and overall risk of mortality (11, 37). The medical consequences of inflammation can be extensive. Therefore, it is crucial to determine the cause of inflammation to ensure effective treatment. (1, 7, 38). Identifying the cause enables a diagnosis to be confirmed and the most suitable treatment to be administered.

1.1.1 Biomarkers of inflammation

The increase in inflammatory diseases is a global health concern, and several studies have been conducted to identify the biomarkers of inflammation (10). Biomarkers are either a chemical, physical or biological parameter that can be used to detect and compute disease progression or treatment outcomes in preclinical research and clinical diagnosis (10). Biomarkers are of great significance as they indicate changes in the state of proteins and other factors that are associated with disease progression. Several broad-spectrum biomarkers have been identified and are currently being used in the clinical diagnosis of inflammatory diseases (10). Although diseases associated with chronic inflammation are among the leading causes of morbidity and health costs, biomarkers for their early diagnosis, prognosis and treatment are inadequate (39).

Blood-based biomarkers are currently used to assess chronic inflammatory diseases and the classification of biomarkers, and their clinical utility have been discussed. Biomarkers are representative of systematic and local tissue inflammation (39). Common plasma biomarkers include C-peptide, insulin-like growth factor 1, estrone, total and free estradiol, total and free testosterone, and C-reactive protein (CRP) (40).

1.1.2 CRP as a biomarker of inflammation

CRP is a homopentameric acute-phase inflammatory protein that is highly conserved and was first discovered in 1930. As a major plasma protein, it plays a significant role in the body's response to inflammation (41, 42). It is representative of a systematic inflammatory response, and is one of the most commonly used biomarkers in clinical science (39). Many studies have assessed whether CRP can be used as a single diagnostic and prognostic biomarker for some diseases. These results have been undisputed because CRP has been found to be highly sensitive (10, 41, 43-45). Studies on diseases and their associated conditions have also highlighted the role of CRP as a crucial research reagent (41, 42). The levels of CRP in the blood provide a more accurate indication of ongoing inflammation and/or tissue injury than other markers of the acute-phase response in most, but not all, disorders (28).

CRP is a crucial component of immunity that recognizes pathogens by binding to surface components to initiate defense mechanisms in the body (41, 43). Owing to its unique binding specificity, it is the initial line of defense against infection (41). During inflammatory conditions,

it shows elevated levels in the blood, and plasma concentrations differ by a minimum of 25%. Plasma CRP levels increase from approximately 1 μg/mL to over 500 μg/mL within one-three days of severe inflammation (42). CRP levels may remain elevated in chronic infections and inflammatory illnesses; however, when the cause of the disease resolves or remits, either on its own or in response to therapy, the CRP concentration quickly returns to normal (41, 46).

However, bacterial infections lead to much more potent production of CRP than localized viral infections (10, 41, 42, 47). In addition, in some important disease conditions, CRP levels remain normal or may be slightly elevated despite continued disease progression (41, 48). However, the extraordinary correspondence of CRP concentrations in response to the severity, degree, and development of various pathologies strongly emphasizes the importance of CRP as a disease marker (41, 49-52). CRP clearance occurs regardless of serum levels or pathophysiological conditions and is monoexponential. Therefore, CRP level is a good marker of disease activity (41, 44, 45, 48).

The unit for reporting laboratory values of CRP varies because there is currently no standard (10, 48, 49, 53, 54). However, CRP levels are generally reported as either mg/dL or mg/L (49, 55-58). Enzyme-linked immunosorbent assays (ELISA), immunoturbidimetry, and antibody-based nephelometric assays have been widely used to measure CRP levels, but these are typically sensitive to concentrations of 5–20 mg/L (58). To detect CRP levels lower than 1.0 mg/L, it is recommended to use high-sensitivity CRP (hs-CRP) assays that are sensitive to lower CRP levels (49, 58-60). Hs-CRP level is generally reported as mg/dL (49, 60). When used for disease risk stratification, the cut-off point for CRP values may differ depending on the disease being assessed, but the consensus is that a CRP level of 1.0 mg/dL indicates marked elevation (49, 55, 61, 62). CRP levels of less than 0.3 mg/dL are considered normal and are observed in most healthy adults. In minor to moderate elevation, CRP levels show concentrations of 1.0 to 10 mg/dL. In severe elevation, CRP levels show concentrations of more than 50 mg/dL (49).

1.2 Coffee consumption

Coffee is a highly commercialized food product commonly consumed globally (63, 64). Coffee was first discovered in Ethiopia between the years 600 and 800, and by the end of the 15th century, the initial coffee house was opened in Mecca. Since then, the coffee consumption has increased

worldwide (64, 65). In coffee year 2022/23, coffee production increased to 168.2 million bags worldwide, signifying a growth of 0.1% (66) The United States, Brazil, Germany, Japan, and Italy are the major consumer countries. However, Finland, Norway, and Sweden have the highest per capita consumption of coffee, consuming twice as much coffee as the United States and Brazil (64, 67).

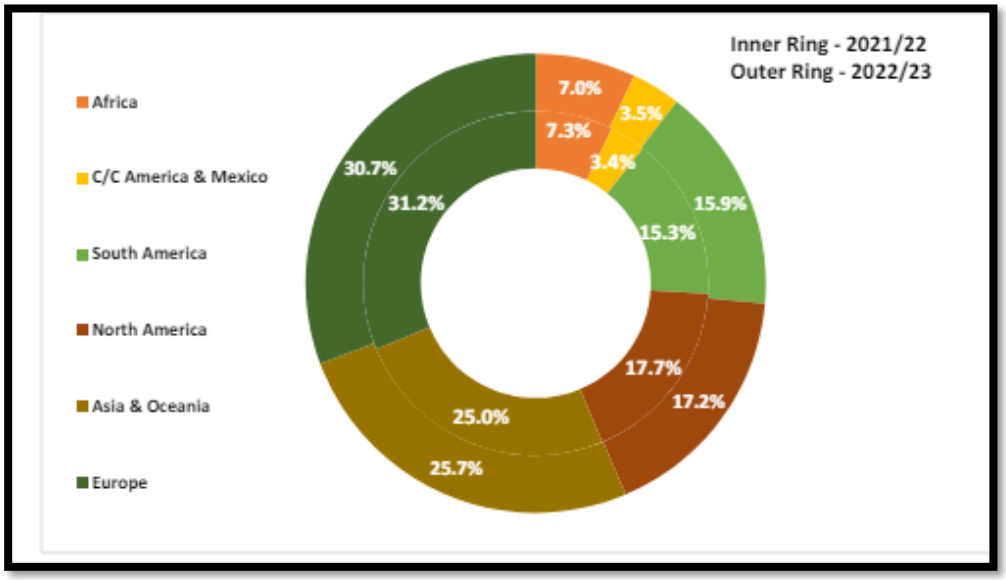

Figure 1: Consumption of Coffee: Regions, Percentage share (66).

As shown in Figure 1, Europe was the highest consumer of coffee from 2021 to 2023. Asia was the second highest consumer of coffee followed by North America. Caribbean, Central America and Mexico had the lowest consumption rates. Africa had the second lowest consumption rate, followed by South America (66).

Many factors have contributed to the constant increase in global coffee consumption, with improved cup quality being the prime factor (64, 68, 69). Cup quality is a systematic approach for evaluating of the aroma and flavor of coffee beans to ensure that the final product has the highest quality (70). Better farming practices, wider selection of coffee breeds and awareness of the health benefits of coffee contribute to this continuous growth in coffee consumption (64, 68). There are two main species of coffee that are produced commercially namely, Coffea arabica and Coffea canephora, accounting for approximately 60% and 40% of the total coffee consumption

worldwide (64, 71). Currently, coffee is classified as a functional food mainly because of its high antioxidant compound content and beneficial biological properties (64, 72).

Coffee contains different complex mixtures of bioactive compounds depending on its type (63). Roasting and processing methods also determine the specific composition of these compounds (63, 73). The bioactive compounds in coffee, such as caffeic acid, chlorogenic acids, trigonelline, diterpenes, and melanoidins, affect the human body (63, 65, 73). Chlorogenic acids constitute the major proportion of polyphenolic compounds found in coffee and are known to exert therapeutic effects on oxidative stress (63, 67, 74). Polyphenols have also been generally associated with improved health outcomes (75, 76).

Caffeine, one of the main bioactive compounds found in coffee, has been explored in several pharmacokinetic studies to better understand its metabolism and absorption (63). It the most frequently consumed psychoactive drug worldwide (73, 77, 78), and one of the most studied substances in the food industry (77). Caffeine is naturally found in coffee, tea, and chocolate. Synthetic caffeine is now widely added to products to improve alertness and energy levels (77, 79). Caffeine is almost completely absorbed into the bloodstream upon ingestion, with 20% of caffeine consumed being absorbed in the stomach, while the remaining 80% occurs in the small intestine (63, 80, 81). The method used to brew coffee determines the amount of caffeine that is consumed. The consumption of caffeine has been linked to numerous biological effects. Topping the list is the stimulation of the central and sympathetic nervous system after coffee consumption, leading to increased alertness (67, 82, 83).

Coffee also contains two diterpenes, cafestol and kahweol, which have been found to have anticarcinogenic and hepatoprotective properties (67, 84). These compounds are however weakly soluble in water and can be trapped by filters (67, 85). Thus, they are mainly found in unfiltered coffee, and sometimes in espresso. Despite their anticarcinogenic and hepatoprotective properties, cafestol and kahweol have been found to increase serum cholesterol levels, leading to an increased risk of coronary heart disease (CHD) (67, 85, 86).

Consumption of coffee has traditionally been associated with unhealthy lifestyle choices, such as smoking, alcohol consumption, and poor eating habits (85, 87). Nonetheless, recent studies have highlighted the positive effects of consuming coffee and its possible associated benefits on health (12, 40, 67, 85, 88, 89). Studies on coffee consumption and its potential benefits in

reducing the risk of developing chronic diseases are on the rise because of the global increase in chronic diseases (67, 73, 85).

Coffee consumption has existed for centuries because of its perceived positive effects on health. The U.S. Food and Drug Administration deems it safe for healthy adults to consume up to 400 milligrams of caffeine daily, which is roughly equivalent to 4 cups of brewed coffee (90). Nonetheless, people may react differently to caffeine and other chemical compounds in coffee. Due to the high consumption of coffee globally, it is of utmost interest both from a public and scientific outlook to evaluate the possible benefits and negative effects it may have on chronic diseases (85, 91). The importance of coffee consumption has been repeatedly debated, largely because of the potential negative aspects being hypothesized (66, 70, 80). For instance, high coffee consumption has been linked to side effects such as anxiety, insomnia, psychomotor agitation, and restlessness (92). The conclusions regarding whether coffee is beneficial to health remain mixed and vary between outcomes (67, 73, 85, 89).

1.3 Association between coffee consumption and inflammation in women and men and the risk of chronic diseases

Various studies have explored the association between coffee consumption and the risk of inflammation, yet results are inconsistent (12, 67, 73, 78, 89, 93-99). Some studies have reported that significant changes in inflammatory responses that were promising are likely to be associated with prolonged coffee intake (63, 67, 100, 101). In addition, consuming 3-4 cups of coffee daily is associated with the greatest benefits (102).

In a systematic review of 15 clinical trials to assess the association between the consumption of coffee or caffeine and serum concentrations of inflammatory markers, regular coffee consumption was found to be associated with a reduced risk of low-grade inflammatory conditions (99).

Three studies with large sample sizes included in a meta-analysis revealed a consistent finding among European and American women, as well as Japanese men, highlighting significant inverse associations between coffee consumption and CRP levels. On the other hand, European men showed a positive association between these two variables. (94). However, the other studies included in the meta-analysis showed no significant association (94).

In studies assessing the relationship between coffee consumption and concentrations of plasma biomarkers, coffee consumption has been linked to favorable profiles of several biomarkers in important metabolic and inflammatory pathways that underlie common chronic diseases (63, 85, 100). It was found to be a rich source of many components that promote antioxidant activity in humans (67, 85). Summarized evidence also indicates that coffee, owing to its abundant antioxidant properties, can reduce biomarkers of inflammation when consumed regularly (63, 67, 99).

Similarly, studies have indicated that regular coffee consumption can help reduce the risk of developing type 2 diabetes and some cancers (98, 103). In a study conducted on healthy women and women with type 2 diabetes, it was also found that filtered coffee consumption was inversely correlated with markers of inflammation and endothelial dysfunction (104). In a population-based cohort study investigating the association between coffee consumption and the incidence of Parkinson disease, it was observed that an inverse exposure-response relationship exists between coffee consumption and Parkinson's disease (105).

The consumption of unfiltered types of coffee, such as French press and boiled coffee has been found to be associated with increased risks of developing chronic diseases (67, 85, 86). In a Greek study, moderate to high consumption of boiled coffee was also linked to increased CRP levels (104). In a Norwegian study of 12 000 healthy men who were heavy drinkers of coffee, coffee consumption was found to be a major determinant of plasma homocysteine level, which is a risk factor for heart disease (106). A similar study conducted in Greece has confirmed these findings (107).

Based on the literature that has been assessed, moderate daily filtered coffee consumption was not linked to an increased risk of developing chronic diseases (63, 89). Conversely, available data reveal that the antioxidant activity of coffee may be inversely associated with the risk of certain chronic diseases such as type 2 diabetes mellitus, CHD, and Parkinson's disease (85, 87, 105). Although few clinical studies have reported how inflammatory biomarkers respond to coffee consumption, the available information points to the beneficial effects of coffee consumption on the improvement of inflammation markers. The emphasis, however, is on the prolonged consumption of coffee and preferably filtered coffee (63, 89).

1.4 Rationale for the study

The association between coffee consumption and chronic inflammation has been explored in several studies (40, 63, 85, 89, 96, 100, 101, 104, 108). However, few clinical studies have reported how inflammatory biomarkers respond to coffee consumption, and sex-specific associations have been sparsely explored (63). Women and men respond differently in their immunological responses to foreign antigens and self-antigens (33). Moreover, the incidence and symptoms of inflammatory diseases, as well as their responses to pharmacological treatments, differ substantially between men and women (34).

Very few studies have been conducted on the consumption of other coffee variants, such as espresso and instant coffee. However, these methods of coffee brewing have become increasingly popular. Therefore, it is important to include them in our study to investigate their association with inflammation to bridge the knowledge gap in other studies and to offer relevant information.

The seventh survey of the Tromsø Study (Tromsø7) 2015–2016 has detailed information on coffee consumption on the participants, and as such, has the potential to contribute to the knowledge gap as to how inflammatory biomarkers respond to coffee consumption.

Coffee was first introduced to Norway in 1694. In the early 18th century, coffee became the preferred beverage of the upper class over alcoholic beverages, and it was fashionable to consume coffee in scholarly groups (68, 69). Coffee consumption has rapidly increased, becoming the second-highest per capita consumption in the world (73). With a total population of a little over five million, such high consumption of coffee makes Norway a favorable population for the investigation of the possible effect of coffee consumption on inflammation as any causal association between coffee consumption and inflammation would have a substantial impact on Norwegian public health (109). The study can thus provide information on both rural and urban populations in Northern Norway, which can be generalized to the whole country. Few clinical studies have reported on how inflammatory biomarkers respond to coffee consumption in women and men, and the findings from this study may help to cover the knowledge gap in other studies.

1.5 Aim and research questions

This study aimed to examine the association between coffee consumption and inflammation in women and men from the general population using Tromsø7 data.

Specific research questions were as follows:

1. Is there an association between total coffee consumption and serum CRP levels in women and men from the population-based Tromsø7?
2. Is there an association between different types of coffee consumed including filtered coffee, boiled coffee, instant coffee, and espresso, and serum CRP levels in women and men from the population-based Tromsø7?

2 Materials and methods

2.1 Data Material

The Tromsø Study, anchored at UiT, the Arctic University of Norway (UiT), is Norway's most comprehensive and participatory population study (110). It is based in Tromsø and covers the Troms municipality, which consists of urban (80%) and rural areas (20%). Seven surveys have been conducted since 1974, and over 45 000 people have taken part in one or more of these surveys (110).

2.1.1 Study design and population

This cross-sectional study used data from the population-based Tromsø7 conducted between 2015-2016. In Tromsø7, all inhabitants of Tromsø municipality aged 40 years and older (n = 32 591) were invited. In total 21 083 people attended, yielding an attendance rate of 65 % (110).

A brochure with information about the study was sent by mail to all invited persons. A questionnaire (Q1) and an invitation to complete a full medical screening were included in the mail.

A total of 111 participants who did not attend the first laboratory visit to measure their serum CRP levels were excluded from the study. Further, 6 245 participants who did not answer the four questions about coffee consumption, measured in cups per day were similarly excluded. Participants with missing data on the other variables (n = 2 070) were excluded from the study.

A total of 12 643 participants were included in this study, comprising 6 411 women and 6 232 men (Figure 2).

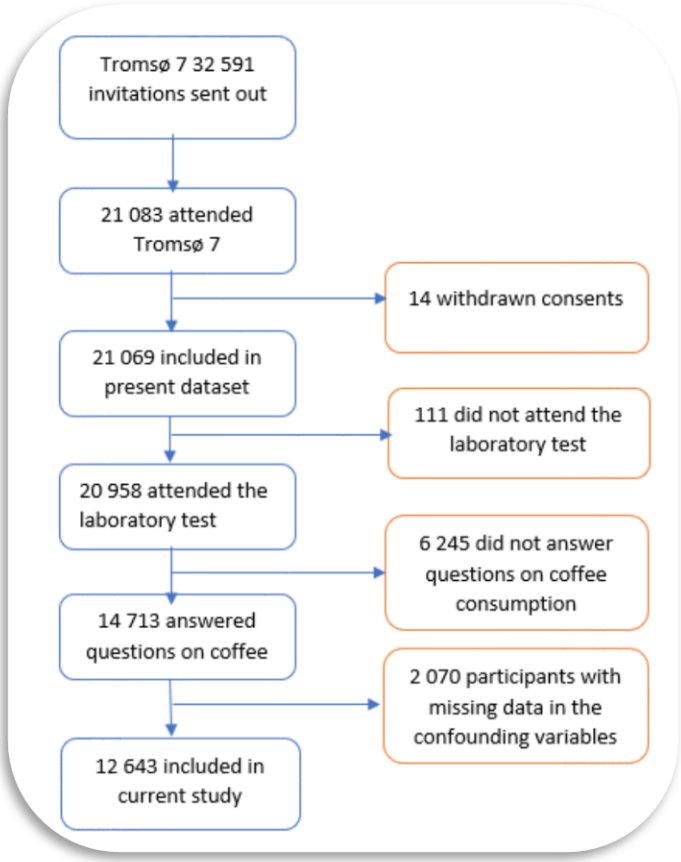

Figure 2: Flowchart of study sample The seventh survey of the Tromsø Study, 2015-2016

2.1.2 Data collection

Data were collected following a standardized protocol using questionnaires, physical examinations, and blood samples. The invitees received unique usernames and passwords alongside information brochures with which they could complete Q1 online before attending the study. Q1 consisted of general questions on sociodemographic factors, lifestyle factors, and health.

During the first visit, the participants underwent physical examinations, and height and weight measurements were obtained. Blood samples were collected by trained personnel during the first laboratory visit. Data collection for Tromsø7 was conducted from March 2015 to October 2016 (111).

2.1.3 Exposure variable: Coffee consumption

Coffee consumption is the exposure of interest in this study. Information on coffee consumption was collected from self-reported food frequency questionnaire (FFQ), which was previously validated using a 24-hour recall (24-HR) dietary assessment method (111, 112).

The FFQ was developed at the University of Oslo (UiO) to measure usual dietary intake in the general Norwegian population (113). It consisted of 261 questions about the average daily intake of 261 different types of food, dietary supplements, and beverages, including alcoholic beverages, during the last year. Coffee consumption variable was divided into four categories: zero consumption, low-moderate consumption (1-2 cups per day), high-moderate consumption (3-5 cups per day), and heavy consumption (≥6 cups per day). There was no standardized cup size in the questionnaire (111).

Total coffee consumption was calculated as the combined consumption of all brewing methods. Q1 had questions asking about four methods of coffee brewing: filtered coffee, boiled coffee/French plunger coffee (coarsely ground coffee for brewing), instant coffee, and espresso-based coffee (from coffee machines, capsules, etc.) (Figure3). Participants were asked to indicate their consumption in cups and to put 0 for the types they did not drink daily (110, 111).

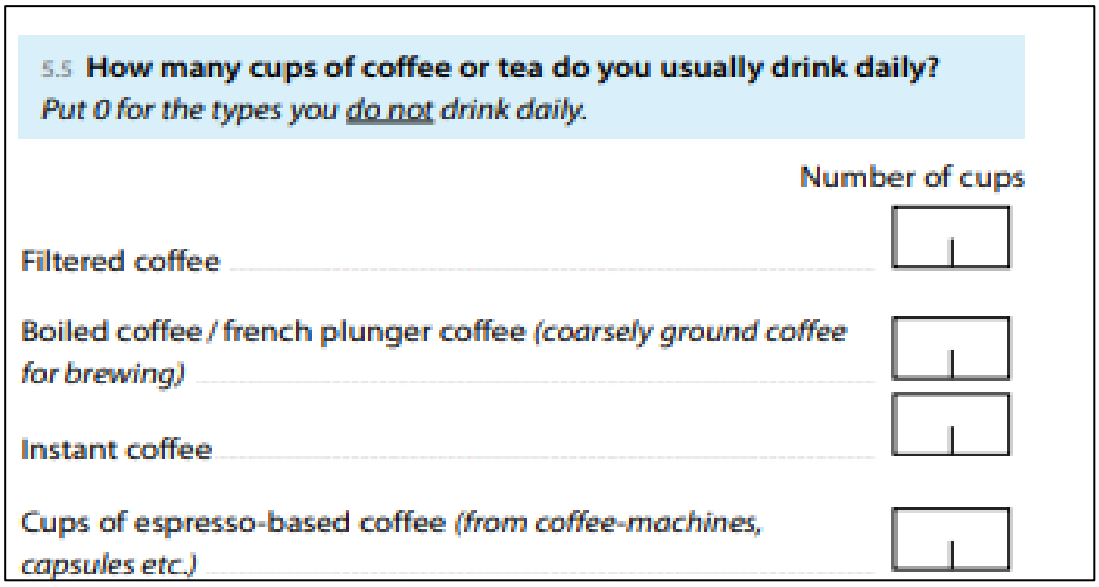

Figure 3: Coffee consumption questions from the food frequency questionnaire (FFQ), The seventh survey of the Tromsø Study 2015-2016 (111).

2.1.4 Outcome variable: Inflammation status

Inflammation, measured as serum CRP levels in mg/dL, was the outcome of this study. During the laboratory visit, non-fasting blood samples were collected using a light tourniquet that was released after venipuncture. The serum samples were processed for 60 minutes in room temperature. These were then centrifuged for 10 minutes at 2000 *g* and transferred within 1 hour to plastic tubes, and kept between 1°C and 10°C.

Inflammation status was categorized into two groups. Serum CRP levels of 1.0 mg/dL or less were considered as normal, and serum CRP levels above 1.0 mg/dL were considered as elevated, following the general consensus in interpreting CRP levels (49).

2.1.5 Covariates

Data on sex and age (years) were obtained from the National Population Registry of Norway. Age was categorized into 10-year age groups, with participants aged 80 years and over categorized into one group due to the small number of participants in these age groups.

Data on educational level (primary/upper secondary/short tertiary/long tertiary), physical activity level at leisure (sedentary/light/moderate/vigorous), smoking status (current/previous/never),

alcohol consumption (never, monthly or less, 2-4 times/month, 2-3 times/week, 4 or more times/week), and soft drink/sugar consumption (rarely/never, 1-6 glasses/week, 1 glass/ day, 2-3 glasses/day, 4 or more glasses per/day) were derived from Q1. Data on the use of antihypertensive medications were also collected from Q1.

During the first clinical examination visit, weight and height measurements were taken with light clothing and no shoes using a Jenix DS-102 scale (DongSahn Jenix, Seoul, Korea). Measurements taken of body weight and height were used to calculate BMI. BMI derived was further grouped into four categories according to the World Health Organization (WHO) BMI criteria: "underweight" for a BMI less than 18.5 kg/m^2, "normal weight" for a BMI of 18.5 to 24.9 kg/m^2, "overweight" for a BMI of 25 to 29.9 kg/m^2, and "obese" for a BMI greater than 30 kg/m^2 (110).

Resting pulse rate and systolic and diastolic blood pressure were measured on the right arm three times at one-minute intervals after 2 minutes of seated rest with a Dinamap ProCare 300 (GE Healthcare, Norway) (111). Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, mean diastolic blood pressure of 90 mmHg or higher, and/or use of antihypertensive medications (114).

2.1.6 Ethical considerations and data safety

Data collection for Tromsø7 was approved by the Regional Committees for Medical and Healthcare Research Ethics (REK, reference 2014/940) and the Norwegian Data Protection Authority. The study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments and complied to International Ethical Guidelines for Biomedical Research Involving Human Subjects and the International Guidelines for Ethical Review of Epidemiological Studies. All the participants were asked to sign consent forms during their attendance. The collected data were securely stored in a EUTRO database, and the process was evaluated and approved by the Norwegian Data Protection Authority (111).

For this specific study, approvals from REK, the Data and Publication Committee (DPU), and the Norwegian Agency for Shared Services in Education and Research (SIKT) was granted in January 2024 following the fulfilment of the necessary safety and ethical requirements.

2.2 Statistical analysis

Stata 18 for Windows was used for all analyses. All analyses were stratified by sex. Statistical significance was set at p-value <0.05.

2.2.1 Descriptive statistics

Baseline characteristics and coffee consumption patterns are presented stratified by sex. Categorical variables are presented as numbers with proportions. Continuous variables are presented as means with standard deviations. Differences across coffee consumption categories in women and men were tested using ANOVA for continuous variables and the Chi square test for categorical variables.

2.2.2 Initial descriptive analysis of inflammation status by coffee consumption level

Descriptive statistics were used to describe the proportion of participants with and without inflammation on total coffee, filtered coffee, boiled coffee, instant coffee, and espresso consumption.

2.2.3 Logistic regression analysis of inflammation status by sex

Binary logistic regression analysis was performed to investigate the association between coffee consumption and inflammation. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated for each of the four coffee consumption categories. Participants who recorded zero (0) cups of daily consumption were used as the reference group. In the first model, ORs were calculated for the association between total coffee consumption and inflammation. Secondly, the associations between the different methods of coffee brewing and inflammation were calculated. The dependent variable, inflammation, was included as a binary outcome (yes or no). Regression models were first adjusted for age and then for age and the other confounders: level of education, BMI, hypertension, physical activity, smoking status, and alcohol consumption. In addition, the brewing method-specific analyses were adjusted for the three other brewing methods. A Directed Acyclic Graph (DAG) was used to differentiate possible confounders. Age, BMI, hypertension, education, physical activity, smoking, alcohol consumption, and soft drink consumption were

the confounders that were identified (115, 116). The DAG was created using DAGitty's online software.

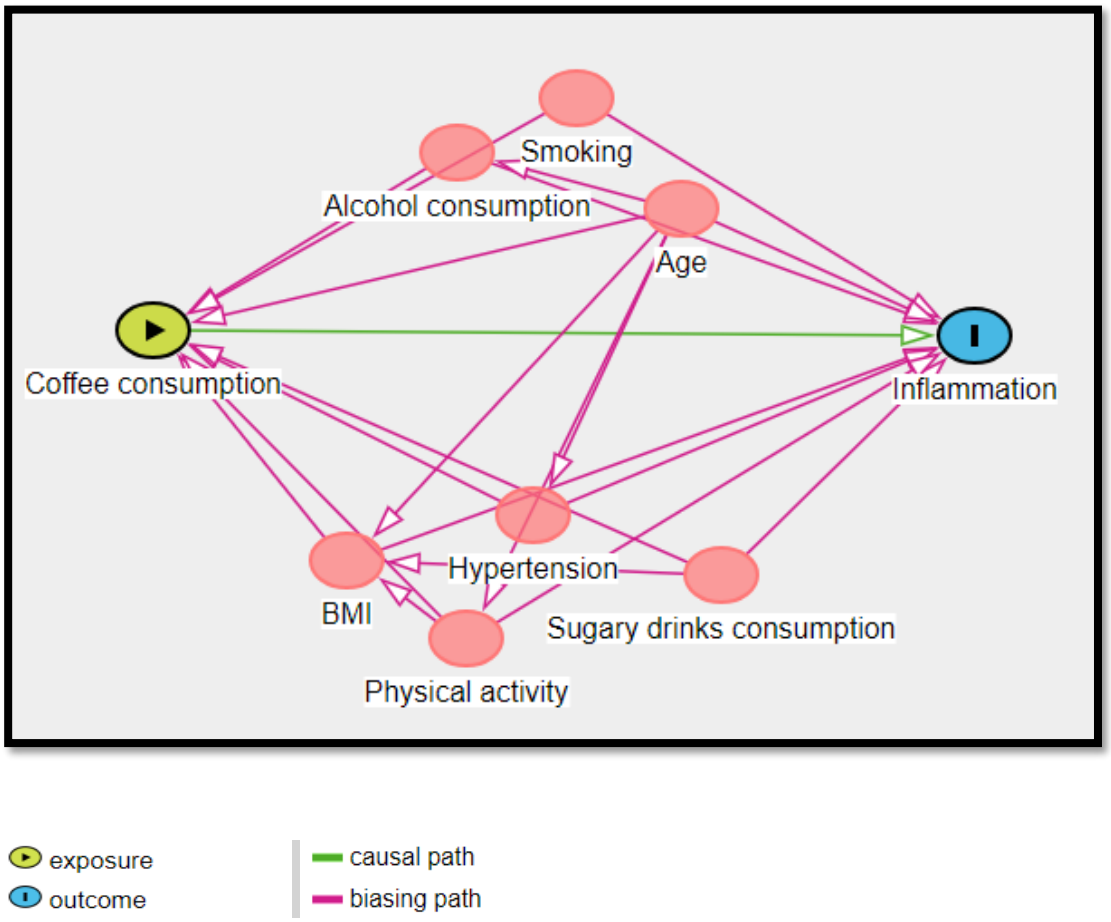

Figure 4: Directed Acyclic Graph (DAG) representing the association between coffee consumption and inflammation and possible confounders(115).

We also created a binary variable for participants that were included and excluded to investigate the differences in characteristics between the two groups. Pearson´s chi-square test (for categorical variables) and Student´s t-test (for continuous variables) were used to examine potential differences according to sex, age, education, BMI, hypertension status, physical activity level, smoking status, alcohol intake and sugary drink intake (Supplementary table 1).

2.2.4 Sensitivity analysis

Coffee consumption is strongly associated with smoking (117, 118) and adjustment for smoking may not fully eliminate the confounding effects of smoking. To check for possible residual confounding by smoking status, we performed a logistic regression analysis for total coffee consumption that was stratified by smoking status in categories (never, former, and current) (Supplementary table 2).

3 Results

3.1 Characteristics of study population according to sex and coffee consumption level

The study population comprised 6 411 (53%) women and 6 232 (47%) men. The mean age was 55.5 years for women and 56.5 years for men (Table 1). Among both women and men, zero coffee consumers were more likely to be younger, and heavy consumers were more likely to be in the age group 50-59 years. Hypertension was most frequently observed in low-moderate and high-moderate coffee consumers compared to zero and heavy coffee consumers in both women and men.

We observed a negative educational gradient in coffee consumption. Heavy coffee consumers in both women and men were more likely to have an upper secondary education, whereas zero consumers of coffee were more likely to have a long tertiary education. Compared to the other levels of coffee consumption, zero coffee consumers in both women and men were more likely to report light physical activity levels. Women and men who were zero coffee consumers were more likely to be never smokers compared to the other coffee consumption levels. Heavy coffee consumers in both women and men were more likely to be current smokers.

Compared to the other levels of coffee consumption, zero coffee consumers were more likely to consume alcohol once a month or less in both women and men. Conversely, heavy coffee consumers in both women and men were more likely to consume alcohol 2-4 times a month. Compared to the other levels of coffee consumption, zero coffee consumers in both women and men were more likely to consume more soft drinks with sugar.

Table 1: Baseline characteristics according to sex and coffee consumption level, the seventh survey of the Tromsø Study 2015-2016 (N = 12 643)

Characteristics, % or mean, (SD)	Women Coffee Consumption Categories					Men Coffee Consumption Categories				
	Zero-consumer (0 cups) N=678	**Low-moderate (1-2 cups)** N=1 166	**High-moderate (3-5 cups)** N=3 260	**Heavy consumer (≥6 cups)** N=1 307	**P value**	**Zero-consumer (0 cups)** N=442	**Low-moderate (1-2 cups)** N=692	**High-moderate (3-5 cups)** N=2 917	**Heavy consumer (≥6 cups)** N=2 181	**P value**
Age, years	49.8 (8.6)	55.6 (11.6)	56.4 (10.5)	56.1 (9.8)	<0.001	52.2 (10.0)	58.4 (12.8)	57.2 (11.2)	56.0 (10.1)	<0.001
Age group					<0.001					<0.001
40-49 years	60.6	38.9	30.4	28.5		51.1	32.0	31.4	31.6	
50-59 years	25.1	24.1	32.0	36.3		26.2	22.8	32.0	31.9	
60-69 years	10.8	22.7	25.3	25.9		15.2	22.7	25.6	25.6	
70-79 years	3.4	11.1	10.4	8.1		6.1	17.9	9.6	9.6	
80+ years	0.1	3.2	1.9	1.3		1.4	4.6	1.2	1.3	
BMI, kg/m2	27.4 (5.9)	26.7 (5.0)	26.5 (4.7)	27.3 (4.8)	<0.001	28.6 (4.8)	27.6 (3.8)	27.6 (3.8)	28.0 (3.9)	<0.001
BMI group					<0.001					<0.001
Underweight	1.2	0.8	0.7	0.9		0	0.3	0.1	0.3	
Normal weight	38.5	43.4	41.4	39.8		23.5	23.1	25.3	21.2	
Overweight	35.0	33.0	37.3	42.0		44.1	51.3	52.4	50.9	
Obese	25.3	22.8	20.5	22.1		32.4	25.3	22.1	27.6	
Hypertension					<0.001					<0.001
No	77.1	66.6	66.3	67.0		66.6	50.6	54.8	57.0	
Yes	22.9	33.4	33.7	33.0		39.4	49.4	45.2	43.0	

Education					<0.001					<0.001
Primary	10.6	17.1	19.8	26.1		17.9	15.9	18.4	23.4	
Upper secondary	24.9	19.5	24.9	29.4		26.7	29.6	28.3	33.5	
Tertiary, short	19.2	19.6	18.9	17.3		21.3	21.0	23.1	21.8	
Tertiary, long	45.3	43.8	36.4	27.4		34.1	33.5	30.2	21.3	
Physical activity					<0.001					<0.001
Sedentary	16.7	12.4	12.0	14.2		18.1	14.6	13.5	15.9	
Light	57.2	65.9	66.5	65.8		50.2	53.9	50.6	51.3	
Moderate	23.0	18.9	18.9	18.2		26.7	27.5	32.1	30.0	
Vigorous	3.1	2.8	2.6	1.8		5.0	4.0	3.8	2.8	
Smoking status					<0.001					<0.001
Never smoker	64.2	56.2	40.6	23.3		64.0	53.3	46.8	31.4	
Current smoker	7.5	5.5	11.0	30.3		9.7	7.1	7.5	22.2	
Previous smoker	28.3	38.3	48.4	46.4		26.3	39.6	45.7	46.4	
Alcohol consumption					<0.001					<0.001
Never	0.3	0.5	0.4	1.0		0.5	0.3	0.2	0.2	
Monthly or less	49.1	32.2	25.7	31.7		41.6	26.9	19.1	18.9	
2-4 times/ month	33.6	37.6	40.9	42.1		35.3	35.3	41.8	45.4	
2-3 times/ week	13.4	23.7	26.8	21.2		16.3	27.4	30.7	28.0	
4 or more times/ week	3.5	6.0	6.2	4.0		6.3	10.1	8.2	7.5	
Soft drinks/ sugar					<0.001					<0.001
Rarely/never	77.4	84.4	85.0	82.6		63.8	68.5	69.3	64.9	
1-6 glasses/ week	17.7	13.8	14.0	16.0		26.0	26.8	27.6	30.6	
1 glass/ day	2.4	1.0	0.6	1.1		5.7	2.9	2.4	3.2	
2-3 glasses/ day	1.9	0.8	0.3	0.2		3.6	1.3	0.6	1.1	
4 or more glasses/ day	0.6	0.0	0.1	0.1		0.9	0.5	0.1	0.2	

BMI: Body mass index; SD: standard deviation

Categorical variables are presented as proportions. Continuous variables are presented as means with SD. offee consumption categories: Zero consumption (0 cups), Low-moderate consumption (1-2 cups), High-moderate consumption (3-5 cups), Heavy consumption (≥6 cups).
BMI categories: Underweight (<18.5kg/m^2), Normal weight (18.5-24.9 kg/m^2), Overweight (25-29.9 kg/m^2), Obese (≥30 kg/m^2). Hypertension was defined as mean systolic blood-pressure ≥ 140mmHg and/or mean diastolic blood-pressure ≤90mmHg, and/or taking antihypertensive medications (WHO).
**A more detailed table with numbers and proportions is provided in Supplementary table 3*

3.2 Distribution of women and men according to types of coffee consumed

Filtered coffee was the most frequently consumed coffee, followed by espresso, instant coffee, and boiled coffee in both women and men (Table 2). Women and men who consumed filtered coffee were more likely to consume high-moderate levels of coffee. Those who consumed boiled, instant, and espresso coffee were more likely to consume low-moderate levels of coffee. The highest proportion of zero consumers was most frequently observed in boiled coffee consumption. These trends were similar between women and men.

Table 2: Distribution of women and men according to filtered coffee, boiled coffee, instant coffee, and espresso consumption, the seventh survey of the Tromsø Study 2015-2016 (N = 12 643)

Method of coffee brewing, n (%)	Women				Men			
	Filtered coffee	**Boiled coffee**	**Instant coffee**	**Espresso**	**Filtered coffee**	**Boiled coffee**	**Instant coffee**	**Espresso**
Zero-consumer (0 cups)	2186 (34.1)	5325 (83.1)	5154 (80.4)	4756 (74.2)	1744 (28.0)	5147 (82.6)	5061 (81.2)	4489 (72.0)
Low-moderate (1-2 cups/ day)	1405 (21.9)	687 (10.7)	873 (13.6)	1125 (17.6)	1113 (17.9)	623 (10.0)	738 (11.8)	1000 (16.1)
High-moderate (3-5 cups/ day)	2202 (34.4)	317 (4.9)	313 (4.9)	470 (7.3)	2277 (36.5)	312 (5.0)	334 (5.4)	599 (9.6)
Heavy consumer (≥6 cups/ day)	618 (9.6)	82 (1.3)	71 (1.1)	60 (0.9)	1098 (17.6)	150 (2.4)	99 (1.6)	144 (2.3)

Proportions are calculated by columns.

3.3 Inflammation status according to types of coffee consumption

The mean consumption of coffee per day in women and men was similar for those with and without inflammation (Table 3). Women and men without inflammation were more frequently high-moderate consumers of coffee in total, and low-moderate and high-moderate consumers of filtered coffee. For the consumption of boiled coffee, instant coffee, and espresso, majority of the population did not consume them either in the no inflammation or inflammation group. We observed a negative trend in coffee consumption in boiled coffee, instant coffee, and espresso consumption.

Table 3: Distribution of inflammation status according to total, filtered coffee, boiled coffee, instant coffee, and espresso consumption for women and men in the seventh survey of the Tromsø Study 2015-2016 (N = 12 643)

	Women		**Men**	
Coffee consumption	No inflammation CRP ≤ 1.0 mg/dL	Inflammation CRP>1.0 mg/dL	No inflammation CRP ≤ 1.0 mg/dL	Inflammation CRP>1.0 mg/dL
N (%)	3 433 (53.5)	2 978 (46.5)	3 279 (52.6)	2 953 (47.4)
Mean consumption, m(SD)	3.9 (2.8)	3.9 (3.1)	4.9 (3.1)	5.0 (3.3)
Total consumption				
Zero consumption (0 cups)	318 (9.3)	360 (12.1)	229 (7.0)	213 (7.2)
Low-moderate (1-2 cups/day)	616 (17.9)	550 (18.5)	352 (10.7)	340 (11.5)
High-moderate (3-5 cups/ day)	1841 (53.6)	1419 (47.7)	1595 (48.6)	1322 (44.8)
Heavy consumer (≥6 cups/ day)	658 (19.2)	649 (21.8)	1103 (33.6)	1078 (36.5)
Filtered coffee				
Zero consumption (0 cups)	1087 (31.7)	1099 (36.9)	909 (27.7)	835 (28.3)
Low-moderate (1-2 cups/day)	805 (23.5)	600 (20.1)	601 (18.3)	512 (17.3)
High-moderate (3-5 cups/ day)	1238 (36.1)	964 (32.4)	1242 (37.9)	1035 (35.1)
Heavy consumer (≥6 cups/ day)	303 (8.8)	315 (10.6)	527 (16.1)	571 (19.3)
Boiled coffee				
Zero consumption (0 cups)	2859 (83.3)	2466 (82.8)	2694 (82.2)	2453 (83.1)
Low-moderate (1-2 cups/day)	393 (11.5)	294 (9.9)	358 (10.9)	265 (9.0)
High-moderate (3-5 cups/ day)	146 (4.3)	171 (5.7)	154 (4.7)	158 (5.4)
Heavy consumer (≥6 cups/ day)	35 (1.0)	47 (1.6)	73 (2.2)	77 (2.6)
Instant coffee				
Zero consumption (0 cups)	2743 (79.9)	2411 (81.0)	2669 (81.4)	2392 (81.0)
Low-moderate (1-2 cups/day)	502 (14.6)	371 (12.5)	392 (11.9)	346 (11.7)
High-moderate (3-5 cups/ day)	158 (4.6)	155 (5.2)	168 (5.1)	166 (5.6)
Heavy consumer (≥6 cups/ day)	30 (0.9)	41 (1.4)	50 (1.5)	49 (1.7)
Espresso				
Zero consumption (0 cups)	2482 (72.3)	2274 (76.4)	2297 (70.1)	2192 (74.2)
Low-moderate (1-2 cups/day)	648 (18.9)	477 (16.0)	566 (17.3)	434 (14.7)
High-moderate (3-5 cups/ day)	268 (7.8)	202 (6.8)	345 (10.5)	254 (8.6)
Heavy consumer (≥6 cups/ day)	35 (1.0)	25 (0.8)	71 (2.2)	73 (2.5)

**Proportions are calculated by columns.*

3.4 The association between coffee consumption and inflammation

A total of 2978 (46.5%) women and 2953 (47.4%) men had inflammation, with CRP levels of 1.0 mg/dL or higher.

In women, compared to zero coffee consumers, the adjusted odds of having inflammation were 27% lower for low-moderate coffee consumption, 43% lower for high-moderate coffee consumption, and 41% lower for heavy coffee consumption (Table 4). The adjusted odds of inflammation were 26% lower for low-moderate, 39% lower for high-moderate, and 33% lower for heavy consumption of filtered coffee in women. For the consumption of instant coffee, the adjusted odds of inflammation were 29% lower for low-moderate consumers, and 25% lower for high-moderate consumers. Odds of inflammation in women with heavy consumption of instant coffee were similar to that for zero consumers. Similarly, the adjusted odds of inflammation were 23% lower for high-moderate consumption of espresso. Odds of inflammation for espresso consumption at either low-moderate or heavy consumption were similar to that for zero consumers. No association was observed between boiled coffee consumption and inflammation in women.

In men, we found no association between coffee consumption and inflammation, either by total coffee consumption or coffee type consumed.

Our results from the sensitivity analysis showed that excluding smokers had no effect on the results (Supplementary table 1).

Table 4: Odds ratios (ORs) with 95 % confidence intervals (CI) of inflammation status according to total and types of coffee consumption in women and men from the seventh survey of the Tromsø Study 2015-2016 (N = 12 643)

	Total coffee consumed		Filtered coffee		Boiled coffee		Instant coffee		Espresso	
	Age-adjusted	Multi-variable[a]	Age-adjusted	Multi-variable[b]	Age-adjusted	Multi-variable[b]	Age-adjusted	Multi-variable[b]	Age-adjusted	Multi-variable[b]
	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI	OR 95% CI
Zero consumers	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Women										
Low-moderate (1-2 cups/ day)	0.69 (0.57-0.83)	0.73 (0.59-0.90)	0.71 (0.62-0.82)	0.74 (0.63-0.86)	0.94 (0.76-1.05)	0.95 (0.79-1.14)	0.79 (0.69-0.92)	0.71 (0.61-0.84)	0.89 (0.78-1.02)	0.97 (0.83-1.13)
High-moderate (3-5 cups/ day)	0.58 (0.49-0.69)	0.57 (0.47-0.70)	0.72 (0.64-0.82)	0.61 (0.53-0.71)	1.02 (1.03-1.63)	1.00 (0.77-1.31)	1.02 (0.81-1.23)	0.75 (0.58-0.97)	0.91 (0.75-1.10)	0.77 (0.62-0.97)
Heavy consumer (≥6 cups/ day)	0.75 (0.62-0.91)	0.59 (0.47-0.73)	0.96 (0.80-1.15)	0.67 (0.54-0.83)	1.45 (0.93-2.26)	0.76 (0.46-1.27)	1.36 (0.84-2.20)	1.03 (0.61-1.74)	0.86 (0.51-1.45)	0.59 (0.34-1.05)
Men										
Low-moderate (1-2 cups/ day)	0.94 (0.74-1.19)	1.05 (0.81-1.36)	0.90 (0.77-1.05)	0.95 (0.80-1.12)	0.84 (0.71-1.00)	0.85 (0.71-1.02)	0.96 (0.82-1.12)	0.93 (0.79-1.11)	0.87 (0.76-1.01)	0.93 (0.80-1.08)
High-moderate (3-5 cups/ day)	0.82 (0.67-1.00)	0.96 (0.77-1.19)	0.88 (0.78-1.00)	0.89 (0.77-1.03)	1.09 (0.87-1.38)	1.02 (0.80-1.31)	1.04 (0.83-1.30)	0.91 (0.71-1.16)	0.85 (0.71-1.01)	0.86 (0.71-1.05)
Heavy consumer (≥6 cups/ day)	0.99 (0.80-1.21)	0.95 (0.76-1.20)	1.15 (0.99-1.34)	0.94 (0.79-1.13)	1.09 (0.78-1.50)	0.83 (0.58-1.19)	1.04 (0.69-1.55)	0.84 (0.55-1.29)	1.21 (0.87-1.70)	0.91 (0.63-1.30)

[a]Adjusted for covariates. [b]Adjusted for covariates and mutually adjusted for the consumption of coffee brewed with the other three methods.

3.5 Characteristics of included and excluded individuals

A total of 12 643 (60%) participants were included, and 8 426 (40%) were excluded from this study (Supplementary table 2). The two groups had similar BMI, physical activity levels, and soft drink consumption patterns. However, compared with the participants excluded from the study, those who were included were more likely to be women, younger, have higher education, and consume alcohol more often.

4 Discussion

4.1 Scientific discussion

In this study, total coffee consumption was associated with a lower risk of inflammation in women but not in men. We further found an association between filtered coffee, instant coffee, and espresso consumption and a lower risk of inflammation in women; however, no association was found for boiled coffee consumption. High-moderate consumption of coffee in women was associated with the lowest risk of inflammation.

Our findings are in line with those of various studies that reported that coffee consumption is inversely associated with inflammation (40, 63, 85, 89, 96, 101, 104, 108). In a dose–response meta-analysis conducted by Moua et al., an inverse association was found between coffee consumption and CRP level (94). A total of 11 studies were included in the meta-analysis, with six studies including both women and men, two included only women and three included only men (100, 119-121). Three studies were conducted in Asia, three in the United States, and five in Europe. The study participants were similar to our study participants, as they included both women and men from Europe. However, the studies included in the meta-analysis involved younger participants aged 18 years and over as opposed to the current study with participants aged 40 years and over. Three of the studies included in the meta-analysis investigated associations separately by sex (94). An inverse association between coffee consumption and CRP levels among European women and Japanese men was reported, but a positive association was observed in European men (94). However, our study found no significant association between coffee consumption and CRP level in men.

From the meta-analysis, of studies that included only women, coffee consumption was found to be inversely related to CRP (100, 119). In the studies that included only men, no association between coffee consumption and CRP was found in one study (94, 100). In the second study with only men, they found that heightened acute inflammatory response to mental stress was positively associated with coffee consumption in men (94, 120). However, they concluded that the results could be as a result of residual or undetected confounding (120). The third study with only men however investigated the association between tea consumption and CRP, but not coffee consumption (94, 121).

Moua et al. also reported that a previous meta-analysis of the association between coffee consumption and blood CRP levels showed no associations, but substantial evidence of heterogeneity between studies was observed (94, 122). They further mentioned that cup volume was not considered in the study (94). This could be the reason for the conflicting results, in addition to women and men being analyzed together.

Rebello et al., reported that the habitual consumption of coffee has beneficial effects on the health status of participants, particularly on insulin sensitivity in a cross-sectional study using data from the Singapore Prospective study-2 (SP2) (96). However, coffee consumption was not found to be associated with CRP levels, in contrast to the current findings. This difference could be largely due to variation in cup volume owing to differences in geographical location, leading to different biological effects of coffee (94). In addition, the associations were not investigated separately for women and men.

Both low-moderate and high-moderate consumption of instant coffee, and high-moderate consumption of espresso were associated with lower risks of inflammation in women in our study. In a cross-sectional study that included 730 healthy women and 663 women with type 2 diabetes, it was found that a higher consumption of filtered coffee (≥2 cups per day) was associated with lower plasma levels of CRP in both healthy and diabetic women (101). An inverse association between filtered coffee consumption and markers of inflammation in women was also found in another study (102).

In a study estimating the association between coffee and subclinical inflammation biomarkers, including CRP, higher habitual coffee intake, including filtered coffee and espresso, was similarly found to be associated with lower circulating levels of CRP (123). A systematic review of 15 clinical studies has revealed that consuming coffee over several weeks is generally associated with a lower risk of inflammation (99). O'Keefe et al. also reported that habitually consuming 3-4 cups of coffee habitually was safe and linked to the most benefits (102). However, they did not stratify the analyses according to sex.

The ATTICA Greek study reported results contrary to ours (124). They found a positive association between moderate to high coffee consumption and increased inflammation (124). The differences in socio-demographic characteristics between the study populations could be

the first reason for this difference. Coffee consumption patterns differ between Greece and Norway. Similarly, as cup volume varies by geographical location, the number of bioactive compounds consumed is affected, and subsequently, their biological effects (94). Secondly, the consumption of only filtered coffee in the ATTICA study was very low (8% of women and 12% of men) compared to our current study (66% of women and 72% of men). Most participants reported drinking both filtered and unfiltered coffee; therefor it was not possible to make comparisons between the different types of coffee (124).

In addition, all types of reported coffee, including instant coffee, brewed coffee, Greek-type coffee, cappuccino, and filtered coffee, were combined, and not analyzed separately. An important factor to consider is that, in Greece, the two most consumed coffee types are Greek-type coffee, which is a type of boiled coffee, and instant coffee (125, 126). Studies have shown that boiled coffee contains higher levels of diterpenes (67, 84). Since the types of coffee consumed were not analyzed separately, it is possible that coffee consumption that was reported by the study participants was dominated by these two types of coffee, leading to a positive association between moderate to high coffee consumption and increased inflammation. In our analyses, we did not find any association between the consumption of boiled coffee, and instant coffee at high-moderate and heavy consumption levels. This could partly explain the conflicting conclusion in the ATTICA study.

4.1.1 Pathophysiological considerations explaining sex differences

In the regulation of physiology and pathology, sex has been identified as a major variable which has led to the inclusion of sex differences in biomedical research (127). Many diseases affect both sexes disproportionally. It has been well established that the severity and progression of diseases that affect the immune system, specifically inflammation differ strongly between sexes regarding disease pattern and therapy (33, 34, 36, 127). This is mainly because sex is a biological variable that affects immune system functions (33). Sex chromosomes and hormones influence the regulation of immune responses in the body (34). As women and men have different sex chromosomes and hormones, it is apparent that there are differences in how each sex reacts to foreign stimuli.

Effective immunity is dependent on a well-coordinated immune response controlled by genetics, the environment, and hormones that modify the response to pathogens or tissue damage in a sex-specific manner (36). It is therefore not surprising that the incidence and severity of inflammatory diseases are sex-biased given that inflammation that is unresolved is caused by innate and adaptive immune responses that are strongly influenced by sex (127).

The bioactive compounds in coffee, such as caffeic acid, chlorogenic acids, trigonelline, diterpenes, and melanoidins are among the constituents of coffee and have been widely researched due to their potential effects on health (75, 76, 128, 129). Genetic differences between the two sexes can influence the metabolism effects of these compounds (128). Phenolic compounds in coffee are likewise metabolized differently in women and men (128). CYP1A1, CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A4, CYP3A5, NAT2, and XO are a group of drug-metabolizing enzymes involved in the metabolism of caffeine (130, 131). CYP1A2 has been reported to be responsible for over 95% of the initial metabolism of caffeine (132). Men appear to have higher amounts of CYP1A2 than women (130, 133). Several studies conducted on drug metabolism have also found that the activities of CYP2B6, CYP2A6, and CYP3A are higher in women than in men. However, the activity of the enzymes CYP2D6 and CYP2E1 in addition to CYP1A2 have been reported to be higher in men (128, 134, 135).

These differences between women and men may help explain why we found significant associations between coffee consumption and inflammation in women but not in men.

4.2 Methodological considerations

4.2.1 Study design

A cross-sectional study design was used to assess the association between coffee consumption and inflammation in both women and men. Although cross-sectional studies are useful in investigating associations at a given point in time, they are innately limited in demonstrating causality (136). As such, when interpreting the results of this study, associations and not causality should be used, as it is not possible to infer a causal relationship. However, in the present study, the exposure variable, usual coffee consumption, was estimated for a period in

the past, whereas serum CRP levels were measured at the first laboratory visit during data collection. This helps to follow the timeline and address temporality in our study.

4.2.2 Selection bias

Selection bias occurs due to any systematic error in selecting the study participants or factors that affect participation in the study (137). It arises because of the study participants not being representative of the general population from which the sample was taken, leading to systematic differences between participants and non-participants. Consequently, the association between exposure and outcome may differ between those in the study and those who are not. In instances of low participation, several issues can arise, especially if there are differences in socio-demographic characteristics between responders and non-responders.

In Tromsø7, the high response rate of 65%, coupled with the fact that all inhabitants aged 40 years and over were invited, increased the internal validity of the study, ensuring that the participants in the study are representative of general population. However, the non-attendance of the 35% could introduce selection bias into the study if there were systematic differences between the participants and non-participants. Non-responders in a survey are usually different from the study participants in both socio-demographic and lifestyle aspects (138), which can consequently affect the measured association. There is also the possibility that more healthy, middle-aged, and physically active individuals participated in the study than older individuals with poorer health, creating a healthy participant bias (139).

Notwithstanding, the Tromsø7 sample has been reported to be representative of the Tromsø population (111, 138, 140). A study (138) comparing the sociodemographic characteristics among participants with non-participants found that the mean age of participants and non-participants were similar. It also found that men and participants with a shorter tertiary education were less likely to participate. However, in the present study, men are equally represented in the study sample with the proportion of men being 49.3%. Moreover, participants with longer tertiary education among women made up the largest proportion, while in men, they were the second largest proportion after upper secondary education. Thus, our study

sample defies these generalizations, making the findings more representative of the general population of Norway.

Excluding participants with missing data could reduce the power size of the sample. However, the number of participants with missing data on the covariates was low (14%) in the current study. From our analysis on the included and excluded participants, we found that participants who were included in the study were younger, had long longer education and drank more alcohol. However, we had enough participants in each coffee category to produce statistically significant results (Supplementary table 2).

4.2.3 Information bias

In epidemiological studies, information bias arises because of systematic errors in measuring the exposure and/ or outcome variables or covariates. It occurs during data collection and can result in either differential or non-differential misclassification (137). In non-differential misclassification, the errors in the measurement of an exposure are the same for participants with and without the outcome. In differential misclassification however, the errors in the measurement of an exposure differ between participants with and without the outcome (137).

In this study, information on coffee consumption and some covariates was collected from the self-reported FFQ (111). Although the FFQ has been validated (111), it is still susceptible to recall bias and measurement errors, as with any self-reported dietary assessment tool. As such, a misclassification, precisely non-differential misclassification, is possible to some degree. However, the FFQ used in the current study was validated with a 24-hours dietary recall assessment method. This method can capture a thorough report of the dietary intake of responders over the last 24 hours (113). It has also been recommended by the European Food Safety Authority (EFSA) as the preferred method for validating food intake for adults (141).

The use of online questionnaires also improved data quality and reduced risk of misclassification through reduced administrative burden. Using online questionnaire also made it possible to have a hierarchal structure of the questionnaires with less participant burden (111).

In Tromsø7, information on the consumption of other types of coffee like cappuccino, café latte, macchiato, and decaffeinated coffee were absent as these methods of brewing coffee were

not included in the questionnaires. It is therefore possible to underestimate the total coffee consumption for some participants, thereby resulting in most likely non-differential misclassification.

In addition, there was no standardized cup size in reporting coffee consumption, making it difficult to estimate the exact amount of coffee that was consumed. Over reporting and underreporting of coffee consumption is the greatest concern here because of differences in cup sizes used. However, all participants were from the Troms municipality, and it is likely that similar cup sizes were used.

Self-reported lifestyle factors, which are often included as covariates in studies, are especially prone to measurement errors leading to information bias. Study participants tend to overreport qualities that are deemed positive, such as physical activity, and underreport negative qualities such as smoking and alcohol consumption (142). Apart from age which was collected from the national registry, and BMI and hypertension status that were calculated from measurements taken at the physical examination, the other covariates included in the study were self-reported, thereby contributing to possible misclassification of the study participants.

Notwithstanding, validation studies on self-reported variables have been conducted and found to be accurate (138). Also, a study to assess the validity of self-reported educational level in Tromsø7 found that the reported data was adequately complete and correct (140).

4.2.4 Confounding

In confounding, the effect of the exposure of interest is associated with the effect of another variable thereby obscuring the real effect of an exposure on the outcome (143, 144). The failure to adjust for confounders in analyses can lead to biases in the estimates in both directions, thereby leading to incorrect conclusions (145). In observational studies, residual confounding is a general concern. There are likely to be residual confounders in this study even though we identified possible confounders using a DAG and adjusted for them accordingly in the models. This could be due to measurement error of a confounder, and possible undetected confounders in the study.

We conducted a sensitivity analysis on smoking status to investigate the possible residual confounding by smoking status, which was the most important confounder in our study. Smoking has been strongly associated with coffee consumption in both clinical and epidemiological studies (118, 146-148). More smokers are known to be coffee consumers than nonsmokers (118). In the present study, we also found that heavy consumers of coffee were more likely to be current smokers. However, our results did not change after excluding smokers from the analyses, thus adding robustness to our results.

We used DAG to assist in the selection of covariates for the statistical analyses and to identify potential confounders. This was done to minimize the effects of confounding and help to improve the internal validity of the results (115, 116).

4.2.5 Strengths and limitations

The large sample size of Tromsø7, combined with the high response rate make it a favorable alternative to carry out this research. With a response rate of 65%, the study sample is very likely representative of the population of Tromsø and of a general Norwegian or Nordic population. This is because the Tromsø municipality shares similar demographic qualities with the general population of Norway (138). Due to the high participation level, there were enough participants in each coffee consumption category, allowing us to perform more precise analyses.

By running the analyses sex-specific, we were able to present evidence that is strong and representative of each sex, and not merely due to chance (149). Furthermore, each sex makes up approximately 50% (50.7% women and 49.3% men) of the current study population, so sex-specific findings which are evident can have widespread significance (149). The study thus presents accurate findings for both sexes unlike other studies that combine analyses. From our study, we found that combing analyses for the two sexes would have led to underestimation of the association between coffee consumption in women and the overestimation of the association in men, leading to wrong inferences.

In this study, by including filtered coffee, boiled coffee, instant coffee, and espresso, we have added to current knowledge on the association between the different types of coffee brewing

methods and inflammation. Few studies have been carried out especially on the consumption of espresso, and results are varied (150). Including this method of coffee brew is valuable as its consumption is becoming increasingly popular. In addition, CRP levels were measured by trained laboratory technicians to ensure quality of the data provided. The use of a standardized measurement procedure increases the internal validity of the study. We are therefore confident of the internal validity of the outcome variable.

The main weakness of the present study is the use of a cross-sectional study design, as they are not the best to investigate causality and associations. Cross-sectional studies have also been reported to not be able to investigate the temporality between outcomes and risk factors. The other limitation is most of the data variables being self-reported. However, several studies that have assessed the validity of the Tromsø7 data have reported that the data reported are valid and representative of the Troms municipality population (112, 138, 140). The possibility of information bias in the study can however not be ruled out.

4.2.6 Relevance

This study brings on board sex-specific findings about the association between coffee consumption and inflammation measured by CRP levels. It reiterates the importance of sex specific research and confirms studies that have reported that associations should be explored separately for women and men. It further strengthens the findings of studies that have reported that the moderate intake of coffee, particularly filtered coffee, can have beneficial effects on women's health, by using a heavy coffee drinking population. By including espresso and instant coffee, we provide information on these coffee types that are becoming increasingly popular in Norway and the world at large.

As mentioned previously, Norway is a heavy coffee drinking country, and providing results that are relevant to the population can help shape the public health of the country through appropriate health policies. Our findings may also contribute to a significant impact on disease risk clinically. Furthermore, information from this study could be used in the management of inflammatory diseases through personalized public health interventions.

5 Conclusion

This study indicates that the high moderate (3-5 cups) consumption of coffee, including filtered coffee, instant coffee, and espresso, is associated with lower risk of inflammation in women. We found no associations between coffee consumption and inflammation in men. Further studies are recommended to understand the underlying mechanisms of these sex differences.

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Supplementary tables

Supplementary table 1: Characteristics of those included in vs those excluded from the study sample. The seventh survey of the Tromsø Study 2015-2016 (N=21 069)

Characteristics	Total	Included	Excluded	P value
Sex, N, (%)				<0.001
Women,	11063 (52.5)	6411 (50.7)	4652 (55.2)	
Men	10006 (47.5)	6232 (49.3)	3774 (44.8)	
Age, years				<0.001
	57.3 (11.4)	56.0 (10.8)	59.3 (12.0)	
Age group, n (%)				<0.001
40-49 years	6426 (30.5)	4280 (33.9)	2146 (25.5)	
50-59 years	6032 (28.6)	3716 (29.4)	2316 (27.5)	
60-69 years	5176 (24.6)	3039 (24.0)	2137 (25.4)	
70-79 years	2675 (12.7)	1355 (10.7)	1320 (15.7)	
80+ years	760 (3.6)	253 (2.0)	507 (6.0)	
Education, n (%)				<0.001
Primary/partly second.	4795 (23.2)	2492 (19.7)	2303 (28.6)	
Upper secondary	5748 (27.8)	3471 (27.5)	2277 (28.3)	
Tertiary education, short	4005 (19.4)	2590 (20.5)	1415 (17.6)	
Tertiary education, long	6143 (29.7)	4090 (32.3)	2053 (25.5)	
BMI, kg/m2				<0.001
	27.3 (4.5)	27.3 (4.5)	27.4 (4.6)	
BMI group, n (%)				0.02
Underweight	114 (0.5)	63 (0.5)	51 (0.6)	
Normal weight	6634 (31.5)	4017 (31.8)	2617 (31.1)	
Overweight	9196 (43.7)	5576 (44.1)	3620 (43.0)	
Obese	5125 (24.3)	2987 (23.6)	2138 (25.4)	
Hypertension, n (%)				0.01
No	12506 (59.4)	7795 (61.7)	4711 (55.9)	
Yes	8563 (40.6)	4848 (38.4)	3715 (44.1)	
Physical activity, n (%)				<0.001
Sedentary	2970 (14.6)	1753 (13.9)	1217 (15.8)	
Light	11807 (58.0)	7374 (58.3)	4433 (57.5)	
Moderate	4949 (24.3)	3128 (24.7)	1821 (23.6)	
Vigorous	632 (3.1)	388 (3.07)	244 (3.1)	
Smoking status, n (%)				<0.001
Never smoker	5418 (42.9)	3307 (40.18)	8725 (41.8)	
Current smoker	1665 (13.2)	1236 (15.02)	2901 (13.9)	
Previous smoker	5560 (44.0)	3687 (44.8)	9247 (44.3)	
Alcohol intake, n (%)				<0.001
Never	1690 (8.1)	46 (0.36)	1644 (19.8)	
Monthly/ less frequently	5137 (24.5)	3298 (26.1)	1839 (22.2)	
2-4 times a month	7892 (37.7)	5161 (40.8)	2731 (32.9)	
2-3 times a week	4973 (23.8)	3285 (26.0)	1688 (20.4)	
4 or more times a week	1246 (6.0)	853 (6.8))	393 (4.7)	
Soft drinks/ sugar, n (%)				<0.001
Rarely/never	15497 (76.1)	9554 (75.8)	5943 (77.0)	
1-6 glasses /week	4204 (20.7)	2721 (21.5)	1483 (19.2)	
1 glass per day	436 (2.1)	247 (1.9)	189 (2.5)	
2-3 glasses /day	179 (0.9)	100 (0.8)	79 (1.0)	
4 or more glasses /day	47 (0.2)	21 (0.2)	26 (0.3)	

Categorical variables are presented as numbers with proportions.
Continuous variables are presented as means with standard deviation (SD).

Supplementary table 2: Logistic regression analysis for total coffee consumption stratified by smoking status in categories, The Seventh survey of the Tromsø study 2015-2016

	Women			Men		
Coffee consumption categories	**Never smoker** **OR** **95% CI** **N=2 718**	**Current smoker** **OR** **95% CI** **N= 868**	**Previous smoker** **OR** **95% CI** **N=2 822**	**Never smoker** **OR** **95% CI** **N=2 698**	**Current smoker** **OR** **95% CI** **N=794**	**Previous smoker** **OR** **95% CI** **N=2 730**
Zero consumers (0 cups)	1.00	1.00	1.00	1.00	1.00	1.00
Low-moderate (1-2 cups/ day)	0.69 (0.52-0.91)	0.72 (0.30-1.69)	0.82 (0.56-1.2)	1.11 (0.80-1.56)	0.82 (0.33-2.01)	0.97 (0.61-1.55)
High-moderate (3-5 cups/ day)	0.53 (0.41-0.69)	0.46 (0.23-0.95)	0.68 (0.48-0.95)	0.96 (0.72-1.27)	1.06 (0.52-2.18)	0.90 (0.60-1.36)
Heavy consumer (≥6 cups/ day)	0.62 (0.44-0.87)	0.54 (0.26-1.1)	0.6 (0.42-0.88)	0.96 (0.71-1.30)	1.27 (0.64-2.52)	0.85 (0.56-1.29)

OR: Odds ratio
CI: Confidence intervals

Supplementary table 3: Baseline characteristics according to sex and coffee consumption level, the seventh survey of the Tromsø Study 2015-2016 (N = 12 643)

		Coffee Consumption Categories				
Characteristics	**Total**	**Zero-consumer (0 cups)**	**Low-moderate (1-2 cups)**	**High-moderate (3-5 cups)**	**Heavy consumer (≥6 cups)**	**P value**
Women						
N, (%)	**6411 (53.0)**	**678 (10.6)**	**1166 (18.2)**	**326 (50.9)**	**1307 (20.4)**	
Age, years						<0.001
	55.5 (10.1)	49.8 (8.65)	55.6 (11.6)	56.4 (10.5)	56.1 (9.8)	
Age group, n (%)						<0.001
40-49 years	2227 (34.7)	411 (60.6)	454 (38.9)	989 (30.4)	373 (28.5)	
50-59 years	1969 (30.7)	170 (25.1)	281 (24.1)	1044 (32.0)	474 (36.3)	
60-69 years	1501 (23.4)	73 (10.8)	265 (22.7)	826 (25.3)	337 (25.9)	
70-79 years	596 (9.3)	23 (3.4)	129 (11.1)	338 (10.4)	106 (8.1)	
80+ years	118 (1.8)	1 (0.1)	37 (3.2)	63 (1.9)	17 (1.3)	
Education, n (%)						<0.001
Primary/partly second.	1257 (19.6)	72 (10.6)	199 (17.1)	645 (19.8)	341 (26.1)	
Upper secondary	1590 (24.8)	169 (24.9)	227 (19.5)	810 (24.9)	384 (29.4)	
Tertiary education, short	1202 (18.7)	130 (19.2)	229 (19.6)	617 (18.9)	226 (17.3)	
Tertiary education, long	2362 (36.8)	307 (45.3)	511 (43.8)	1188 (36.4)	356 (27.4)	
BMI, kg/m2						<0.001
	26.8 (5.1)	27.4 (5.9)	26.7 (5.0)	26.5 (4.7)	27.3 (4.8)	
BMI group, n (%)						<0.001
Underweight	53 (0.8)	8 (1.2)	9 (0.8)	24 (0.7)	12 (0.9)	
Normal weight	2552 (39.8)	261 (38.5)	506 (43.4)	1351 (41.4)	434 (33.2)	
Overweight	2388 (37.3)	237 (35.0)	385 (33.0)	1217 (37.3)	549 (42.0)	
Obese	1418 (22.1)	172 (25.3)	266 (22.8)	668 (20.5)	312 (23.9)	
Hypertension, n (%)						<0.001
No	4336 (67.6)	523 (77.1)	777 (66.6)	2160 (66.3)	876 (67.0)	
Yes	2075 (32.4)	155 (22.9)	389 (33.4)	1100 (33.7)	431 (33.0)	
Physical activity, n (%)						<0.001
Sedentary	833 (13.0)	113 (16.7)	144 (12.4)	390 (12.0)	186 (14.2)	
Light	4186 (65.3)	388 (57.2)	768 (65.9)	2169 (66.5)	860 (65.8)	
Moderate	1230 (19.2)	156 (23.0)	221 (18.9)	615 (18.9)	238 (18.2)	
Vigorous	163 (2.5)	21 (3.1)	33 (2.8)	86 (2.6)	23 (1.8)	
Smoking status, n (%)						<0.001
Never smoker	2718 (42.4)	435 (64.2)	655 (56.2)	1323 (40.6)	305 (23.3)	
Current smoker	870 (13.6)	51 (7.5)	64 (5.5)	359 (11.0)	396 (30.3)	
Previous smoker	2823 (44.0)	192 (8.3)	447 (38.3)	1578 (48.4)	606 (46.4)	
Alcohol intake, n (%)						<0.001
Never	33 (0.5)	2 (0.3)	6 (0.5)	12 (0.4)	13 (1.0)	
Monthly/ less frequently	1960 (30.6)	333 (49.1)	376 (32.2)	837 (25.7)	414 (31.7)	
2-4 times a month	2550 (39.8)	228 (33.6)	438 (37.6)	1334 (40.9)	550 (42.1)	
2-3 times a week	1517 (23.7)	91 (13.4)	276 (23.7)	873 (26.8)	277 (21.2)	
4 or more times a week	351 (5.5)	24 (3.5)	70 (6.0)	204 (6.2)	53 (4.0)	
Soft drinks/ sugar, n (%)						<0.001
Rarely/never	5360 (83.6)	525 (77.4)	984 (84.4)	2771 (85.0)	1080 (82.6)	
1-6 glasses /week	948 (14.8)	120 (17.7)	161 (13.8)	458 (14.0)	209 (16.0)	
1 glass per day	62 (1.0)	16 (2.4)	12 (1.0)	19 (0.6)	15 (1.1)	
2-3 glasses /day	34 (0.5)	13 (1.9)	9 (0.8)	10 (0.3)	2 (0.2)	
4 or more glasses /day	7 (0.1)	4 (0.6)	0 (0.0)	2 (0.1)	1 (0.1)	

Men						
N, (%)	**6232 (47.0)**	**442 (7.1)**	**692 (11.1)**	**2917 (46.8)**	**2181 (35)**	
Age, years						<0.001
	56.5 (11.0)	52.2 (10.0)	58.4 (12.8)	57.2 (11.2)	56.0 (10.1)	
Age group, n (%)						<0.001
40-49 years	2053 (32.9)	226 (51.1)	221 (32.0)	917 (31.4)	689 (31.6)	
50-59 years	1747 (28.0)	116 (26.2)	158 (22.8)	777 (26.6)	696 (31.9)	
60-69 years	1538 (24.7)	67 (15.2)	157 (22.7)	755 (25.9)	559 (25.6)	
70-79 years	759 (12.2)	27 (6.1)	124 (17.9)	398 (13.6)	210 (9.6)	
80+ years	135 (2.2)	6 (1.4)	32 (4.6)	70 (2.4)	27 (1.3)	
Education, n (%)						<0.001
Primary/partly second.	1235 (19.8)	79 (17.9)	110 (15.9)	536 (18.4)	510 (23.4)	
Upper secondary	1881 (30.2)	118 (26.7)	205 (29.6)	827 (28.3)	731 (33.5)	
Tertiary education, short	1388 (22.3)	94 (21.3)	145 (21.0)	674 (23.1)	475 (21.8)	
Tertiary education, long	1728 (27.7)	151 (34.1)	232 (33.5)	880 (30.2)	465 (21.3)	
BMI, kg/m2	27.8 (4.1)	28.6 (4.8)	27.6 (3.8)	27.6 (3.8)	28.0 (3.9)	<0.001
BMI group, n (%)						<0.001
Underweight	10 (0.2)	0 (0.0)	2 (0.3)	2 (0.1)	6 (0.3)	
Normal weight	1465 (23.5)	104 (23.5)	160 (23.1)	739 (25.3)	462 (21.2)	
Overweight	3188 (51.2)	195 (44.1)	355 (51.3)	1528 (52.4)	1110 (50.9)	
Obese	1569 (25.2)	143 (32.4)	175 (25.3)	648 (22.1)	603 (27.6)	
Hypertension, n (%)						<0.001
No	3459 (55.5)	268 (66.6)	350 (50.6)	1598 (54.8)	1243 (57.0)	
Yes	2773 (44.5)	174 (39.4)	342 (49.4)	1319 (45.2)	938 (43.0)	
Physical activity, n (%)						<0.001
Sedentary	920 (14.8)	80 (18.1)	101 (14.6)	393 (13.5)	346 (15.9)	
Light	3189 (51.2)	222 (50.2)	373 (53.9)	1475 (50.6)	1119 (51.3)	
Moderate	1898 (30.5)	118 (26.7)	190 (27.5)	937 (32.1)	653 (3.0)	
Vigorous	225 (3.6)	22 (5.0)	28 (4.0)	112 (3.8)	63 (2.8)	
Smoking status, n (%)						<0.001
Never smoker	2700 (43.3)	283 (64.0)	369 (53.3)	1364 (46.8)	684 (31.4)	
Current smoker	795 (12.8)	43 (9.7)	49 (7.1)	218 (7.5)	485 (22.2)	
Previous smoker	2737 (43.9)	116 (26.3)	274 (39.6)	1335 (45.7)	1012 (46.4)	
Alcohol intake, n (%)						<0.001
Never	13 (0.2)	2 (0.5)	2 (0.3)	5 (0.2)	4 (0.2)	
Monthly/ less frequently	1338 (21.5)	184 (41.6)	186 (26.9)	556 (19.1)	412 (18.9)	
2-4 times a month	2611 (41.9)	156 (35.3)	244 (35.3)	1220 (41.8)	991 (45.4)	
2-3 times a week	1768 (28.4)	72 (16.3)	190 (27.4)	896 (30.7)	610 (28.0)	
4 or more times a week	502 (8.1)	28 (6.3)	70 (10.1)	240 (8.2)	164 (7.5)	
Soft drinks/ sugar, n (%)						<0.001
Rarely/never	4194 (67.3)	282 (63.8)	475 (68.5)	2021 (69.3)	1416 (64.9)	
1-6 glasses /week	1773 (28.4)	115 (26.0)	185 (26.8)	806 (27.6)	667 (30.6)	
1 glass per day	185 (3.0)	25 (5.7)	20 (2.9)	71 (2.4)	69 (3.2)	
2-3 glasses /day	66 (1.0)	16 (3.6)	9 (1.3)	16 (0.6)	25 (1.1)	
4 or more glasses /day	14 (0.2)	4 (0.9)	3 (0.5)	3 (0.1)	4 (0.29	

Categorical variables are presented as numbers with proportions. Continuous variables are presented as means with standard deviations. Coffee consumption categories: Zero consumption (0), Low-

moderate consumption (1-2 cups), High-moderate consumption (3-5 cups), Heavy consumption (≥6 cups).

BMI: Body mass index BMI, n (%) Underweight (<18.5kg/m2) Normal weight (18.5-24.9 kg/m2) Overweight (25-29.9 kg/m2) Obese (≥30 kg/m2).

Hypertension was defined as mean systolic blood-pressure ≥ 140mmHg and mean diastolic blood-pressure ≤90mmHg (WHO).

Exercise and physical activity in leisure time over the last year. 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.

Appendix

Appendix 1: Invitation letter from The Tromsø Study 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 folke-helsen 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, lunge-sykdommer, 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 Tromsø-undersøkelsen. 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

Tromsøundersøkelsen er finansiert av UiT Norges arktiske universitet, Helse Nord RHF, Universitetssykehuset Nord-Norge (UNN) samt ulike forskningsfond.

Forsikring

Deltakere i Tromsøundersøkelsen er forsikret gjennom Norsk Pasientskadeerstatning.

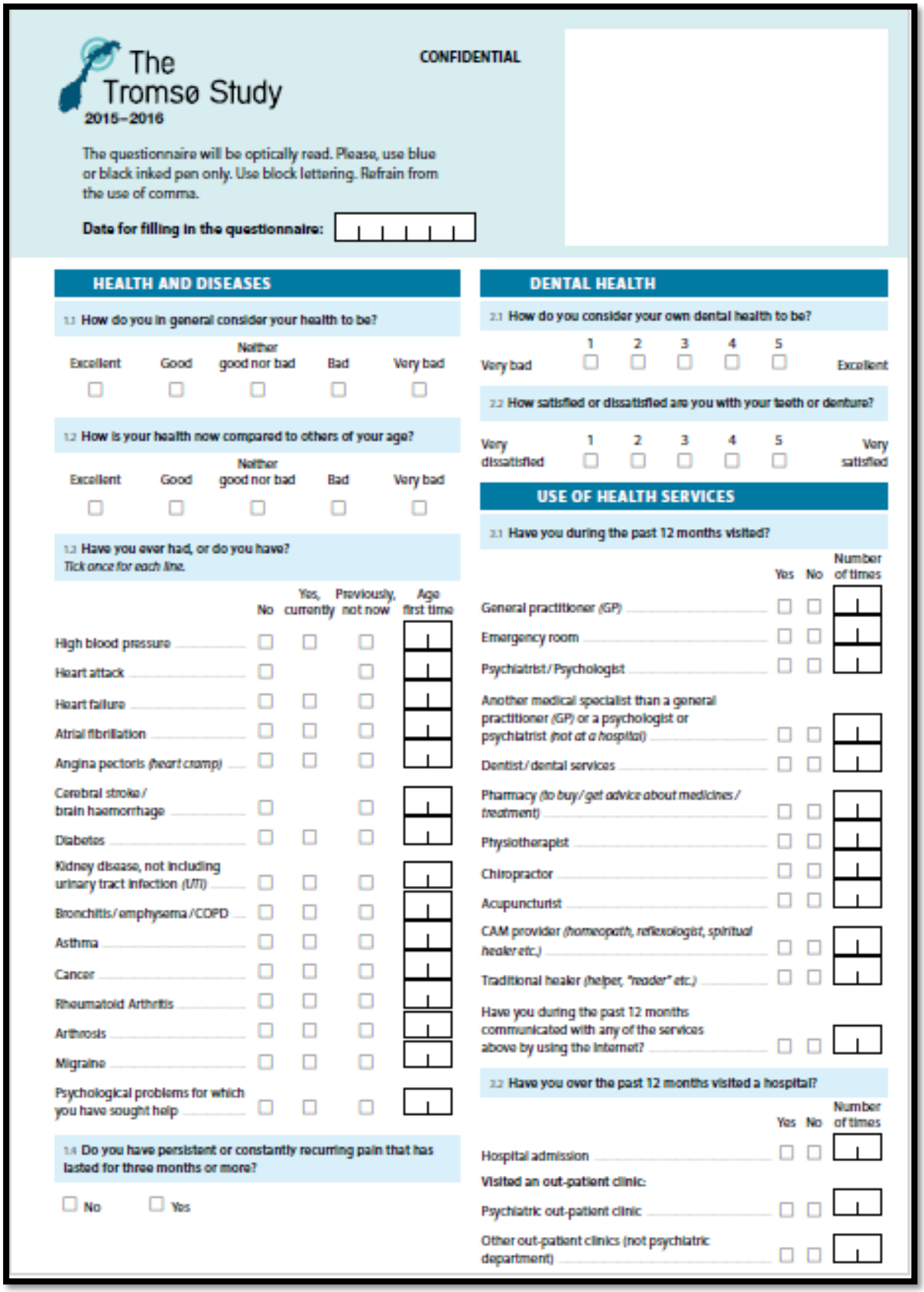
Samtykke til deltakelse i studien

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:
Heilovelen 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 (Q1) from the Tromsø Study 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 of/m?	☐	☐	☐	☐	☐

PHYSICAL ACTIVITY

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

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

Age

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

☐ No ☐ Yes ☐ Uncertain

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

Number

12.4 **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.