UiT The Arctic University of Norway

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Association Between Smoking and Cognitive Function Based on Atrial Fibrillation Status: The Tromsø Study

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ABSTRACT

Background: According to World Health Organization (WHO), the global tobacco smoking prevalence is 22.3% (36.7% for men and 7.8% for women). Cigarette smoking is a risk factor for cancer, cardiovascular diseases, and cognitive decline. The association of smoking and cognitive decline is well documented. Whitehall II Cohort study, Doetinchem Cohort study and many other studies have found that smoking and cognitive decline are associated to each other. As shown by many studies atrial fibrillation (AF) is also the risk factor for cognitive decline.

Purpose of the study: The main aim of this study is to identify the association between smoking and cognitive function based on AF status.

Method: This is a longitudinal study with 3305 participants included from Tromsø6 and Tromsø7 study. SPSS version 26 was used for all the analyses. Means and standard deviation (SD) were calculated for continuous variables whereas number and proportions were presented for categorical variables. T-test and chi-square test were used to calculate the difference between groups. ANCOVA analysis was used to calculate the mean cognitive score among different groups according to smoking habit and AF status. Cognitive test scores were subtracted from Tromsø7 to Tromsø6 to find out the differences in cognitive test scores from Tromsø6 to Tromsø7. Mean change in test scores from Tromsø6 to Tromsø7 was estimated with ANCOVA analysis in three different models. Covariates included in the analysis were baseline test scores, age, sex, education, smoking, physical activity, hypertension, total cholesterol, HDL cholesterol, BMI, myocardial infarction, and HbA1c.

Results: Cognitive function was found to be improved in Tromsø over about 9 years and there was decline in smoking habit. After adjusting for the covariates (model 1, 2 and 3) the result showed that smoking was significantly associated with cognitive decline as shown by digit-symbol coding test and tapping test among those without AF.

Conclusion: Smoking is significantly associated with cognitive decline among people without AF as measured by digit-symbol coding test and tapping test.

Key terminology used:

Smoking, Cognitive decline, Atrial Fibrillation

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Padam Darji

MPH

ACRONYMS

WHO: World Health Organization

AF: Atrial Fibrillation

CVD: Cardiovascular Disease

SBP: Systolic Blood Pressure

DBP: Diastolic Blood Pressure

MCI: Mild Cognitive Impairment

MI: Myocardial Infarction

HDL: High-density lipoprotein

SD: Standard Deviation

CI: Confidence Interval

HbA1c: Hemoglobin A1c

TABLE OF CONTENTS:

List of Tables

List of Figures

CHAPTER I: INTRODUCTION

1.1 Smoking and its prevalence:

The tobacco epidemic claims around 8 million people lives annually, and cigarette smoking is the most common form of tobacco use worldwide (1). According to World Health Organization (WHO), the global tobacco smoking prevalence in 2020 is 22.3% (36.7% for men and 7.8% for women) (1). Among the six WHO regions, Europe holds the highest tobacco smoking prevalence at 28% (38% for men and 19% for women) (2). A 2021 report from Statistics Norway claims that 8% of the people in Norway are smokers, with women at 9% and men at 6% (3).

1.2 Smoking and its health effects:

Smoking is a global problem, however most smoking related deaths occur in low-and middle-income countries (1). Several studies have documented that smoking is hazardous to health and is a risk factor for numerous chronic diseases (4-6). Cigarette when smoked releases several toxic compounds like nicotine, tar, carbon monoxide etc. These compounds induce oxidative stress, and neuroinflammation. These can further result in several negative effects on health in the nervous system. Women with a smoking history may have children who with increased risk of weak performance in school activities, language development and memory(4). Smoking alone contributes to 18% strokes globally(4). Smoking cause endothelial dysfunction in the brain which may promote atherosclerosis and arterial remodeling which increased the risk of stroke and other cerebrovascular disease. Smoking induces pathological changes which may accelerate the development of dementia (4).

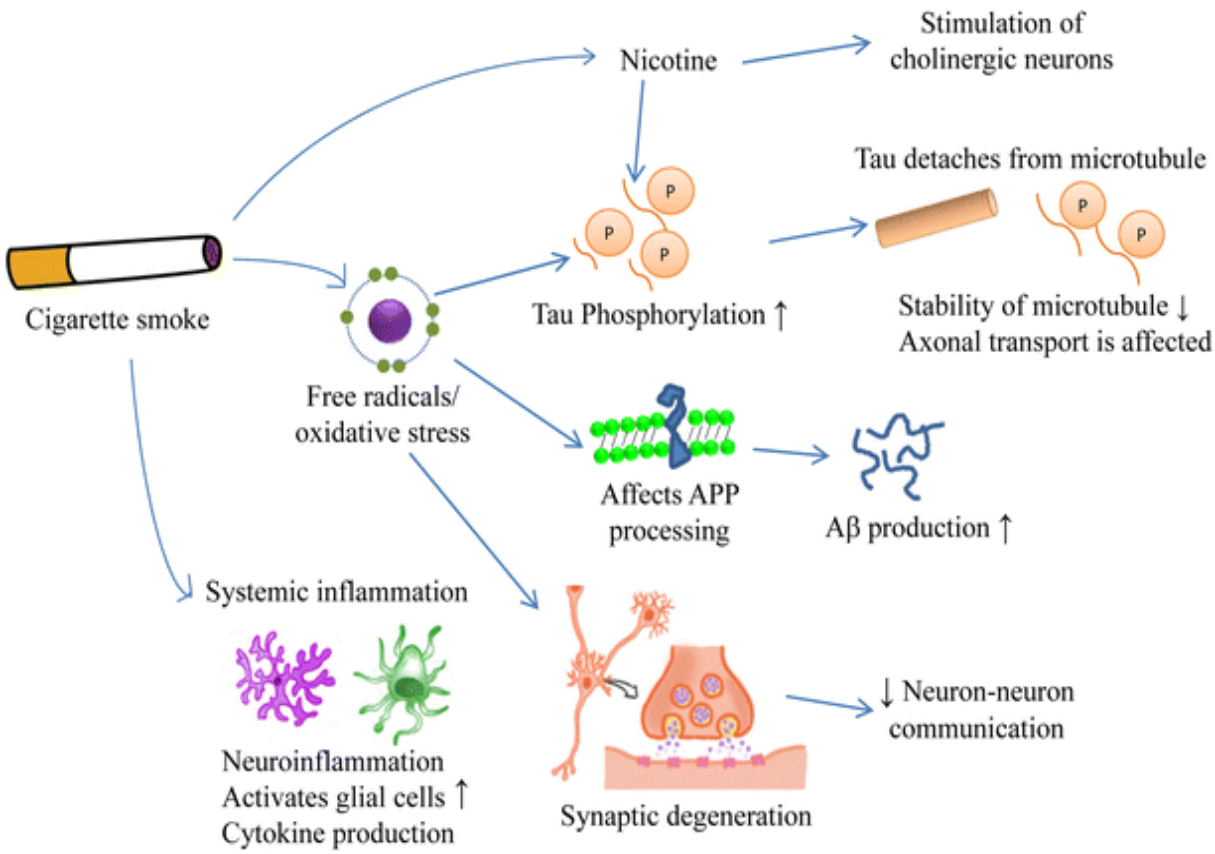

Figure 1: Effects of cigarette smoking in human and rodent (4)

From figure 1, we can understand that cigarette smoking can cause oxidative stress and inflammation which eventually may lead to neuropathological changes in the brain causing several neurodegenerative diseases (4).

Cigarette smoking is a risk factor for cancer, cardiovascular diseases, and cognitive decline (5-7). Smoking affects the normal function of the nervous system. It also causes premature aging and disorder in cognitive function, or cognitive impairment (5). Cognitive impairment is the disorder of intellectual processes including learning, thinking, reasoning, remembering, problem solving, decision-making and attention (8).

1.3 Cognitive Decline:

The proportion of elderly people is growing rapidly. Globally, one in 11 people were aged 65or older in 2019 but that ratio is predicted to be one in six people by 2050 globally(9). It is estimated that one in four people will be aged more than 65 years in Europe and North America by 2050 (9). Aging population is a global phenomenon and higher prevalence of the elderly population will result into higher prevalence of several diseases and complications such as cognitive decline. Cognitive decline is **''***a disorder characterized by impairment of memory, learning difficulties, and reduced ability to concentrate on a task for more than brief periods. There is often a marked feeling of mental fatigue when mental tasks are attempted, and new learning is found to be subjectively difficult even when objectively successful***"** (10). According to a systematic review published in 2020 which included 80 papers from all parts of the world the prevalence of cognitive decline ranged from 5.1% to 41% globally. The prevalence of cognitive decline is highest in South America which accounts for 34% and lowest in Europe which accounts for 12% (11). A study by Johnsen et al. compared cognitive function using the data from Tromsø5, Tromsø6 and Tromsø7 population studies. They concluded that cognitive function has improved in Tromsø among both sexes (12). This same study also identifies education, high blood pressure (BP), smoking, hypercholesterolemia, stroke, alcohol consumption, diabetes, depression, heart attack, physical activity, height, and body mass index (BMI) as influential factors for cognitive function (12). A systematic review which included 20 studies examined the association between vascular risk factors and cognitive decline in patients with dementia in which 50% of the studies found a positive association. 71% of the studies showed that there is no association between hypercholesterolemia and cognitive decline whereas 29% of the studies showed an association. 38% of these studies showed an association between cognitive decline and diabetes mellitus while 46% studies did not find a significant effect on cognitive decline in patients with dementia. This study also suggested that overweight was associated with cognitive decline (13).

1.4 Atrial Fibrillation:

Atrial fibrillation (AF) is a medical condition in which abnormal impulse occurs because electric signals do not start in the sinus node, but in the atria of the heart, which causes abnormal heart rhythm that is irregular. There are different types of AF. These are first diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF and permanent AF (14). According to 2010 Global Burden of Disease Study worldwide estimated prevalence of AF is 596 per 100,000 men and 373 per 100,000 women. It is estimated that the prevalence of AF among the adult population is 1-4% and more than 13% among people greater than 80 years in the USA, Europe, and Australia (15). The prevalence of AF ranged between 0.5% and 1% in the general population in Europe in the year 2000 and in 2014 those numbers have doubled (16). It is estimated that AF cases will reach 18 million by 2060 in Europe (15). According to a Norwegian nationwide study, the prevalence of AF among the population above 18 years was 3.4% (2.8% in women and 4% in men) in 2014 (17).

Aging, hypertension, congestive heart failure, coronary artery disease, valvular heart disease and diabetes mellitus are independent risk factors for AF. Male sex, left ventricular hypertrophy, obesity and excessive alcohol use are other risk factors (18). AF is associated with increased risk of stroke, myocardial infarction, heart failure, dementia, chronic kidney diseases and increased mortality (15). AF has developed as a major public health problems and health care expenditure has been raised enormously in western countries (16).

According to a longitudinal study, AF prevalence among people aged 85 to 89 years was 16% and it is expected to be double in the next 30 years (19). Studies have shown a positive association between the occurrence of AF and cognitive function disorder (19, 20). AF is associated with 40% cognitive decline in participants without a history of stroke (19, 21, 22). According to a study by Xiong et al. variables contributing to cognitive function decline among patients with AF are smoking, age, education, smoking history, NT-pro B type, natriuretic peptide, hemoglobin, and anti-coagulation medication (8).

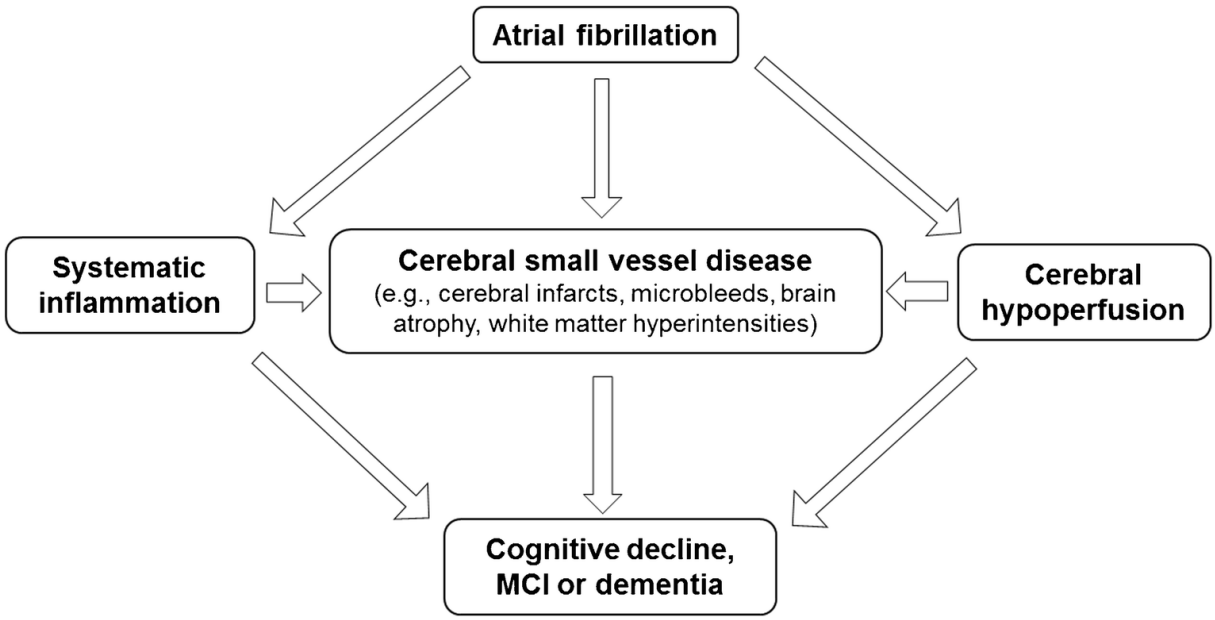

Figure 2: Biological mechanism of atrial fibrillation causing cognitive decline (23)

According to figure 2, AF causes systematic inflammation, cerebral small vessel disease and cerebral hypoperfusion which triggers cognitive decline, mild cognitive impairment (MCI) or dementia (23).

1.5 Association between smoking and cognitive decline:

The association of smoking and cognitive decline is well documented. There are several studies which have identified the risk factors for cognitive decline. Arntzen et al in their study using data from the Tromsø Study has found that smoking was associated with lower cognitive test results (7). According to the Whitehall II Cohort study, cognitive decline (global cognitive, executive function) was higher among current smokers than never smokers. Similarly recent ex-smokers had greater cognitive decline (executive function) than long-term ex-smokers and never smokers (24). The Doetinchem Cohort study conducted in Netherland followed up for 5 years to identify the association between smoking and cognitive decline. In this study, memory function decline was 1.9 times greater among smokers compared to non-smokers, and cognitive flexibility decline was 2.4 greater among smokers than non-smokers, and cognitive decline was 1.7 times greater among smokers than non-smokers (25). The British 1946 birth cohort study revealed that heavy smoking caused cognitive impairment and decline in midlife, and in old age it also caused clinically significant cognitive decline (26). One study based on 15 years long Tromsø data (2001-2016) stated that less smoking in later born cohorts mediated their improvement in cognitive function test by 12.2% in the finger tapping test and by 9% in word test 1. This study suggests that smoking is directly related to cognitive decline (12).

1.6 **Significance of the study:**

It is well documented that smoking is significantly associated to cognitive decline (5, 25, 27) and smoking is one of the risk factors for AF (8). There are various effects of AF and one of the prominent effects is dementia and cognitive decline (19-21). We can find scientific literature about smoking and cognitive decline, cognitive decline and AF, and smoking and AF but still there are limited studies which have researched smoking, cognitive decline, and AF together. Population is ageing (9) with increasing prevalence of several diseases including AF and dementia which is growing as a prominent global epidemic and can lead to decrease quality of life and raised health expenditure. So, this is a study on the association between smoking and cognitive decline in persons with and without AF.

1.7 Purpose of the study

1.7.1 Aim of the study:

The general aim of the thesis was to study the association of smoking and cognitive function based on AF status.

1.7.2 The specific aim of the study was:

To investigate the association between smoking and cognitive function of the population who participated in the Tromsø population studies 6 and 7 based on AF status.

1.8 Research question:

What is the association between smoking and cognitive function based on AF status?

CHAPTER II: MATERIALS AND METHODS

2.1 Study design: The study design of this study is population based longitudinal study.

2.2 Study area and population:

There were high mortality rates for cardiovascular diseases (CVD) in northern Norway during the 1970s. Therefore, the Tromsø Study was initiated in 1974 with an emphasis on modifiable risk factors for CVD (28). It is a prospective cohort study which has been one of Norway's longest lasting surveys with a very high attendance rate among general population. Seven surveys (1974-2016) named Tromsø1 through Tromsø7 have been conducted until now, each 7-8 years apart. Data collection included questionnaires, biological sampling, measurements, and clinical examinations. Total birth cohorts and random samples were invited to participate in the study, and in total 45473 individuals participated in one or more surveys. This study was conducted in the Norwegian municipality of Tromsø, which has the population of around 77,000 as per 2022. Tromsø is dominated by Caucasians of mainly Norwegian origin and it is also home to a Sami minority (29).

Data for this study was taken from the sixth and seventh Tromsø survey. The sixth Tromsø survey (Tromsø6) was conducted in 2007-2008. The total number of participants who participated in this study were 12,984 (men = 6054, women= 6930). All residents of age 40-42 and 60-87, 10% sample of 30-39 and 40% sample of 43-59 were invited to the study. This survey had 65% attendance rate. This study was conducted with two screening studies and several follow-up studies (29).

The seventh survey of the Tromsø study (Tromsø7) was carried out in 2015-2016. All the people who were aged 40 years to 99 residing in Tromsø were invited to participate in the survey. 32,591 people were invited and 21,083 people participated in this survey. This survey had 65% attendance rate. The survey was conducted in two phases (30).

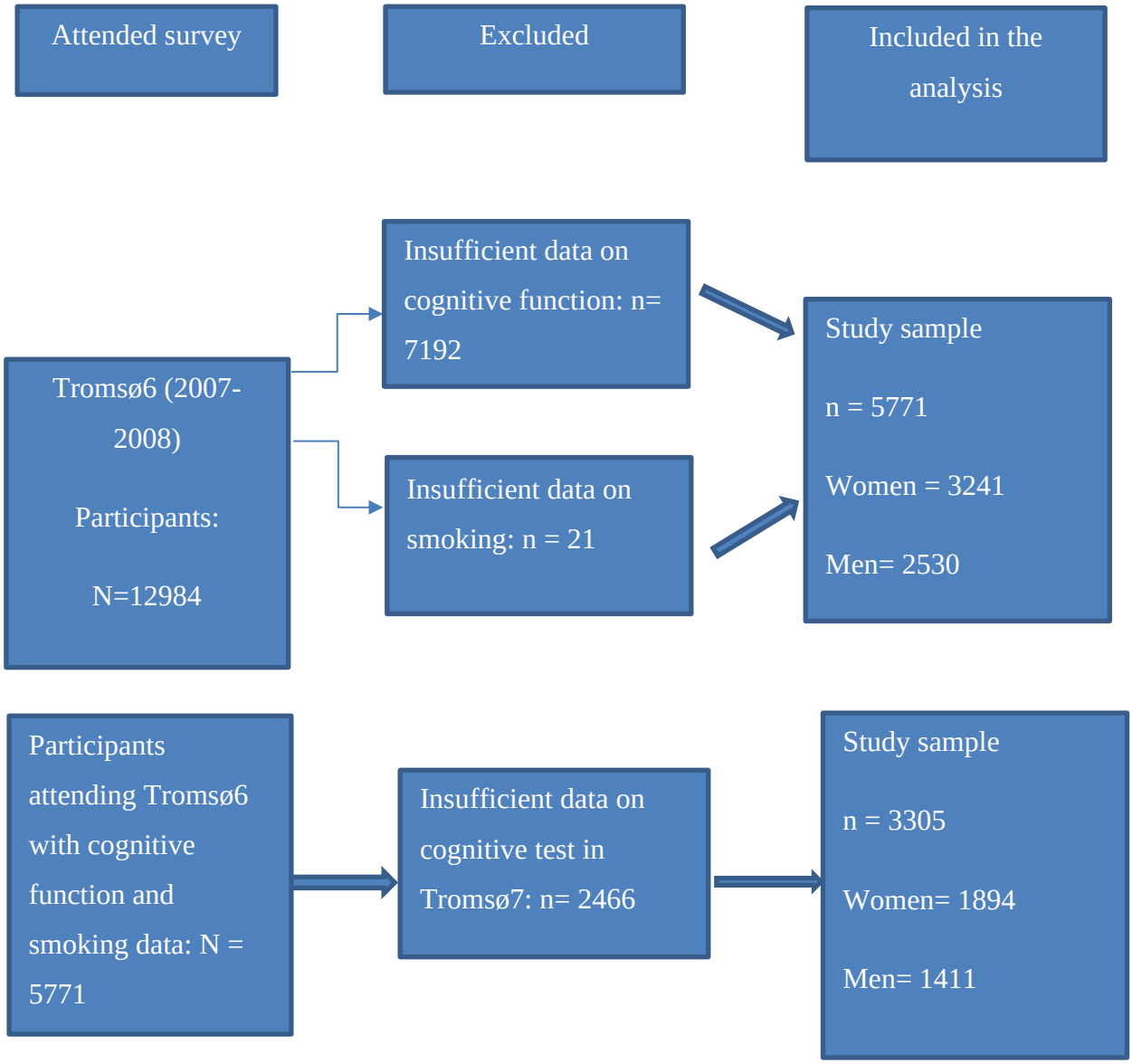

Figure 3: Flowchart of the study population: The Tromsø Study

Among 12,984 participants attending Tromsø6 study, 7192 participants who did not participate in either cognitive test were excluded. Similarly, 21 participants who did not have data for smoking for Tromsø6 study were also excluded. The total number of participants considered for cross-sectional analysis form Tromsø6 were 5771 (men = 2530, women = 3241). Among these 5771 participants, 2466 participants did not attend Tromsø7 or did not participate in either cognitive test in Tromsø7, so those were excluded in the final analysis. Finally, 3305 (men = 1411, women = 1894) participants with repeated measurement in cognitive tests were included for the longitudinal analysis.

2.3 Inclusion Criteria:

The participants who participated in both Tromsø6 and Tromsø7 population study and had cognitive tests performed.

2.4 Exclusion Criteria:

Those participants who have not participated in either of the four cognitive tests in Tromsø6 and Tromsø7 were excluded. Similarly, if participants had insufficient smoking data, they were also excluded.

2.5 Study variables:

Dependent Variable: Cognitive function was the dependent variable of this study. Cognitive function was assessed by four tests in the Tromsø6 and Tromsø7 studies: verbal memory test, digit symbol coding test, finger tapping test and mini-mental state examination.

Verbal memory test: Both surveys made some modifications in Californian Verbal Learning Test and used 12 words memory test. This test measures verbal episodic memory. Subjects were shown 12 nouns written on a board and were pronounced once in 5 second intervals. People were given 2 minutes time and were asked to recall the words (20).

Digit-symbol coding test: This test is a small section of the Wechsler Adult Intelligence test which measures psychomotor speed, attention, and mental flexibility. Rows containing small blank squares were each paired with a randomly assigned number from one to nine. Above these rows, a printed key paired each number with a different nonsense symbol. Following a practice trial, the subjects filled in as many as possible of the blank spaces with the corresponding symbol over a period of 90 seconds (20).

Finger-tapping test: This test was primarily used to examine the psychomotor tempo. Subjects were asked to tap their index finger on a computer four times and tapped number were recorded. The mean number from the last three taps were used. Tapping test was done for both dominant hand and non-dominant hand. The mean value for these two measurements were used during the analysis (20).

Mini-mental state examination: A 30-point questionnaire was used to test several functions like arithmetic, memory, and orientation (29).

Independent variable:

Smoking: Smoking is the most important independent variable in this study. Smoking habit was assessed through a self-administered questionnaire. We used two questions from the questionnaire to make our smoking variable.

Do you smoke sometimes, but not daily? Yes, No

Do you/did you smoke daily? Yes, now/Yes, previously/ Never.

We combined answers from these two questions, recoded, and built three categories for this variable: - ‘‘Never’’, ‘‘Previous smoker’’, ‘‘Current smoker’’. In the final analysis, however, we built two categories ‘‘Never’’, and ‘‘Ever’’. We did this because there were few participants in the ‘‘Current smoker’’ and ‘‘Previous smoker’’ stratified by AF who attended both Tromsø6 and Tromsø7, therefore we combined these categories into one new category ‘‘Ever’’.

Atrial Fibrillation:

AF data were extracted from the diagnosis registry at the University Hospital of North Norway (outpatient clinic excluded), using the following diagnostic codes: ICD-9 codes 427.0-427.99 and ICD-10 codes 147 and 148. Details are given elsewhere (20). AF variables in the dataset was categorized into ‘‘Yes’’ and ‘‘No’. All AF types were merged in the analysis.

Confounders

Age: We had 12 age groups in the dataset and we recategorized the age group into three groups. These were ≤ 64, 65-74 and ≥ 75 years. Continuous data was not provided in the dataset.

Sex: Sex was categorized as men and women.

Alcohol: Alcohol was assessed as intake per drinking session according to second question of Alcohol use disorder identification (31). It was recategorized as no alcohol, 1-2 units, 3-4 units and 5 or more units.

Education: Education was recategorized with technical school and high school diploma as upper secondary school. Thus, education was categorized into four categories such as primary/secondary, upper secondary, tertiary education short (less than 4 years) and tertiary education long (4 years or more).

Physical Activity: We had 4 categories for this variable in our dataset. Reading. watching TV, or other sedentary activity were considered as 'Sedentary'. We defined ''work that requires walking, cycling or other forms of exercise at least 4 hours a week'' as- light physical activity. Then we combined ''participation in recreational sports, heavy gardening etc.'' and ''participation in hard training as sports competitions, regularly several times a week'' and labeled this category as moderate to vigorous physical activity. Thus, we had three categories in this variable, which is sedentary, light, and moderate to vigorous physical activity group.

Myocardial Infarction: This variable was also assessed through questionnaires. This variable had two categories: ''Yes'' and ''No''.

Hypertension: Blood pressure was measured three times at 1-minute intervals after 2 minutes of rest using an automatic device. The mean of last two measurements was used. We had systolic blood pressure (SBP) and diastolic blood pressure (DBP) data for every participant. Questionnaire was used to assess the information on anti-hypertensive medication use. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥ 90 mmHg and/or anti-hypertensive medication.

Total HDL Cholesterol ratio: Non fasting total cholesterol and serum high-density lipoprotein (HDL) cholesterol were analyzed by using enzymatic colorimetric method. The variable Total HDL Cholesterol ratio was formulated by dividing the total cholesterol by HDL cholesterol.

HbA1c: HbA1c was analyzed by high-performance liquid chromatography with variant II (Bio-Rad laboratories, Hercules, California, USA) (32).

Body Mass Index: BMI was calculated as measured body weight/height^2. The categorized variable as: - ''Normal''= < 25 kg/m^2, ''Overweight'' = 25-30 kg/m^2, and ''Obese''= > 30 kg/m^2 were provided in the dataset.

2.6 Statistical Analysis:

SPSS version 26 was used for all the analyses. Means and standard deviation (SD) were calculated for continuous variables. Similarly, numbers and proportions were presented for categorical variables for baseline characteristics. Differences between groups were calculated by t-test and chi-square test for continuous variables and categorical variables respectively.

ANCOVA analysis was used to calculate the mean cognitive score among never smokers, current smoker, and previously smoker stratified by AF for four different cognitive tests. Age, sex, and education were adjusted during this analysis.

Cognitive test scores were subtracted from Tromsø7 to Tromsø6 to find out the differences in test scores from Tromsø6 to Tromsø7. Mean change in test scores from Tromsø6 to Tromsø7 was estimated with ANCOVA analysis in three different models. The first model was analyzed with adjustment of the socio-demographic variables such as age, sex, education, and baseline cognitive test scores. In the second model we added all the variables related to the lifestyle and health measurement such as total HDL cholesterol ratio, hypertension, physical activity, BMI and, alcohol use for adjustment. In the last model we added diseases such as myocardial infarction, and HbA1c status, for adjustment. These variables were added in the model because they were either significant in univariate analysis or they were found significantly associated in previous literature. All the assumption for ANCOVA analysis was checked for before the analysis. The model assumptions were confirmed by graphical inspection of residuals. As no age and sex interaction were found and due to power, sex-combined analysis was performed. A two-sided $p<0.05$ was considered statistically significant.

3 Ethical Consideration:

With the permission from UiT the Arctic University of Norway data were requested from the data delivery committee at the Tromsø Study. Ethical consent from the participants was taken during the Tromsø Study and since the data was anonymous, no further ethical approval was required to conduct this study. The data is saved in One Drive and will be deleted after the completion of the study.

CHAPTER III: RESULT

Table 1: Unadjusted baseline characteristics of the participants by atrial fibrillation status. The Tromsø Study: Tromsø6

Baseline Characteristics	**Atrial Fibrillation**		**P-value**
	Yes (294)	No (5477)	
Age, years	21.1% (62)	57.8% (3164)	
35-64	39.1% (115)	28.7% (1571)	< 0.001
65-74	39.8% (117)	13.5% (742)	
75-85			
Sex			
Men	61.2% (180)	42.9% (2350)	< 0.001
Women	38.8% (114)	57.1% (3127	
Education			
Primary/Secondary School	44.9% (128)	35.2% (1897)	
Upper Secondary high school	31.9% (91)	33.5% (1809)	0.002
College/University < 4 years	14% (40)	15.8% (852)	
College/University ≥ 4 years	9.1% (26)	15.5% (837)	
Smoking			
Never	36.4% (107)	34.2% (1872)	< 0.001
Previous	50% (147)	42.9% (2349)	
Current	13.6% (40)	22.9% (1256)	
Alcohol Units (per drinking session)			
Never	21.3% (60)	12.7% (676)	
1-2	62.8% (177)	62.4% (3326)	0.024
3-4	13.5% (38)	20.4% (1086)	
5 or more	2.5% (7)	4.6% (246)	
Physical Activity			
Sedentary	28.3% (68)	18.7% (920)	< 0.001
Light activity	59.6% (143)	64.6% (3183)	
Moderate to vigorous	12.1% (29)	16.7% (821)	
Systolic Blood Pressure, mmHg	141.0 (22.9)	141.5 (23.3)	< 0.001
Diastolic Blood Pressure, mmHg	78.4 (10.67)	78.1 (11.7)	< 0.001
Hypertension			
Yes	76.2% (224)	60.2% (3296)	< 0.001
HDL Cholesterol, mmol/l	1.43 (0.47)	1.56 (0.45)	< 0.001
Total Cholesterol, mmol/l	5.20 (1.21)	5.78 (1.1)	< 0.001
Triglycerides, mmol/l	1.56 (0.82)	1.5 (0.83)	0.269
HbA1c, mmol/l	6.02 (0.84)	5.74 (0.65)	< 0.001
Anti-hypertensive medication	54.9% (156)	28.2% (1523)	< 0.001
BMI, kg/m^2			
Normal	20.1% (59)	32.8% (1797)	<0.001
Overweight	52.4% (154)	46.1% (2522)	
Obese	27.6% (81)	21.1% (1155)	
Verbal memory test	5.8 (1.86)	6.52 (1.97)	< 0.001
Digit symbol coding test	30.2 (12.8)	39.1 (13.4)	< 0.001
Mini mental state examination	27.7 (2.2)	28.2 (1.68)	0.0004
Tapping test	47.4 (12.4)	51.9 (10.7)	<0.001

The unadjusted baseline characteristics of the respondents are summarized in Table 1.

Socio-demographic variables:

AF was most prevalent in age group 75-85 at 39.8%, almost equally prevalent in the 65-74 age group at 39.1%. 35-64 age group had 21.1% of AF prevalence. Higher AF prevalence was found in men than women. 61.2% of those with AF were men whereas only 38.8% were women. People who were least educated had high prevalence of AF. The table showed that 44.9% of the participants who had AF had primary/secondary school education, 31.9% of the participants with AF had secondary school education, 14% of the participants with AF had college university education less than 4 years and 9.1% of the participants with AF had college university education of 4 years or more. Age, sex, and education was significantly associated with AF.

Lifestyle behavior variables:

Previous smokers had highest AF prevalence. 50% of those with AF were previous smokers. 62.8% of those with AF used to drink 1-2 units of alcohol per drinking session. 60% of the participants with AF used to do only light physical activity.

Disease and health measurement variables:

Among those with AF 76.2% had hypertension. Both Total cholesterol and HDL cholesterol was higher among the people without AF. Triglycerides and glucose level were higher among the people with AF. Among those with AF 52.4% were overweight, 27.6% were obese and 20.1% were normal. Smoking, alcohol, BMI were significantly associated with AF. Total and HDL Cholesterol and, HbA1c was significantly associated with AF. Triglyceride was not significantly associated with AF.

Cognitive test:

Cognitive test score was greater among people who did not have AF. In verbal memory test people without AF had mean cognitive score 6.52 and with AF had 5.8. Symbol test showed that mean cognitive score was greater among people without AF (39.1). Mini mental state examination showed that mean cognitive score was greater among people without AF (28.2). Similarly, people without AF had mean cognitive score of 51.9 and among those with AF had mean cognitive score of 47.4 as shown by tapping test. All cognitive tests were significantly associated with AF.

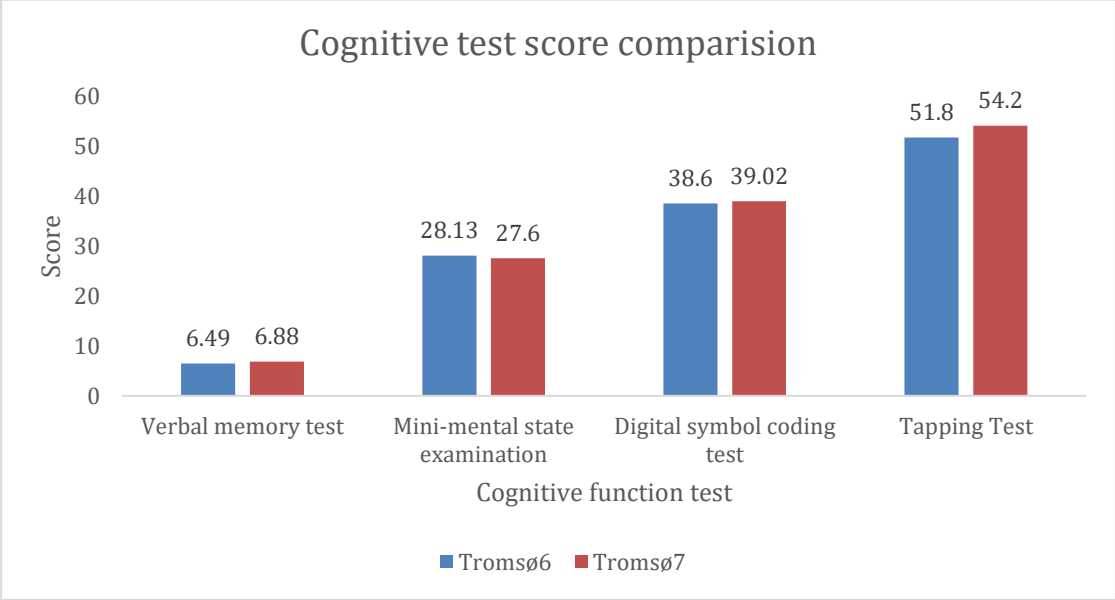

Figure 4 comparing mean cognitive test score between Tromsø6 and Tromsø7 participants

Figure 4 demonstrated that mean cognitive score has increased among the Tromsø Study participants from 2007 to 2015-16. Mean verbal memory test score in Tromsø6 was 6.5 which has upstretched to 6.9 in Tromsø 7. Digital symbol coding test has shown that mean score was 38.6 in Tromsø6 and was increased to 39.0 Tromsø7. Tapping test has shown that cognitive score has increased to 54.2 in Tromsø7 from 51.8 in Tromsø6. However, there was slight decrease in cognitive score as shown by mini-mental state examination.

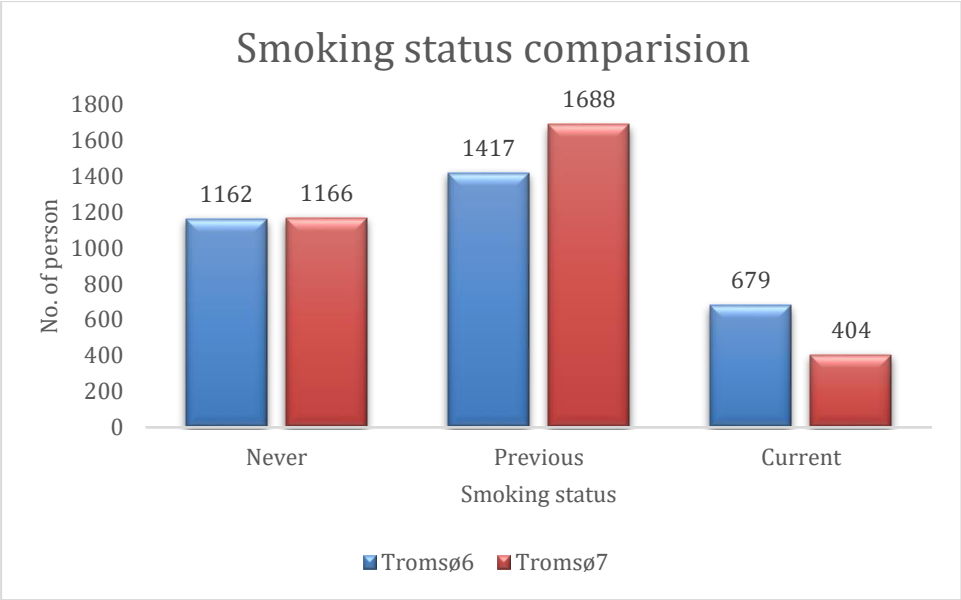

Figure 5 comparing smoking status between Tromsø6 and Tromsø7 studies (participants attending both studies)

Figure 5 demonstrated that the number of current smokers were decreasing in Tromsø and there are lots of participants who have quit smoking from 2007 to 2015-16. Previous smoker was 1417 in Tromsø6 which sharply increased to 1688 in Tromsø7. Current smoker has reduced to 404 in (Tromsø7) from 679 (Tromsø6).

Table 2: Mean cognitive test scores (95% CI) in Tromsø6 and Tromsø7 (subsample with repeat measurement) by smoking status stratified by atrial fibrillation status. The Tromsø Study

	Tromsø6 (n=5711)		**Subsample with repeated measurement Tromsø7 (n= 3305)**	
	Mean (CI)	P-Value	Mean (CI)	P-Value
Verbal memory Test, No AF				
Smoking				
Never	6.57 (6.4, 6.6)	0.569	7.02 (6.91, 7.13)	0.398
Previous	6.52 (6.4, 6.5)		6.92 (6.82, 7.02)	
Current	6.54 (6.4, 6.6)		6.94 (6.8, 7.08)	
Verbal memory test, Yes AF				
Smoking				
Never	5.92 (5.5, 6.2)	0.109	6.18 (5.83, 6.53)	0.243
Previous	5.78 (5.4, 6.0)		6.15 (5.86, 6.44)	
Current	5.23 (4.6, 5.7)		5.64 (5.06, 6.21)	
Digit symbol coding test, No AF				
Smoking				
Never	39.49 (39.0, 39.9)	0.022	40.49 (39.76, 41.23)	0.033
Previous	39.36 (38.91, 39.8)		39.34 (38.67, 40.01)	
Currently	38.44 (37.8, 39.0)		39.13 (38.18 40.08)	
Digit symbol coding test, Yes AF				
Smoking				
Never	29.61 (27.5, 31.6)	0.030	32.82 (30.95, 34.7)	0.130
Previous	31.65 (29.8, 33.4)		33.10 (31.56, 34.65)	
Current	26.44 (22.9, 29.9)		29.69 (26.68, 32.69)	
Mini mental state examination, No AF				
Smoking				
Never	28.18 (28.09, 28.26)	0.898	27.64 (27.52, 27.77)	0.737
Previous	28.17 (28.1, 28.25)		27.67 (27.56, 27.79)	
Current	28.15 (28.04, 28.25)		27.72 (27.56, 27.89)	
Mini-mental state examination, Yes AF				
Smoking				
Never	27.66 (27.1, 28.22)	0.693	27.22 (26.67, 27.77)	0.197
Previous	27.56 (27.07. 28.05)		26.99 (26.53, 27.44)	
Current	28.06 (27.02, 29.10)		26.24 (25.34, 27.14)	
Tapping test, No AF				
Smoking				
Never	52.57 (52.13, 53.01)	<0.001	55.11 (54.67, 55.55)	<0.001
Previous	52.27 (51.88, 52.66)		54.54 (54.14, 54.94)	
Current	51.02 (50.48, 51.56)		53.08 (52.51, 53.65)	
Tapping test, Yes AF				
Smoking				
Never	47.33 (45.05, 49.61)	0.174	52.96 (51.36, 54.56)	0.481
Previous	47.99 (46.06, 49.91)		51.69 (50.39, 52.98)	
Current	44 (40.29, 47.70)		52.26 (49.73, 54.79)	

- *Age, sex, and education covariates were adjusted for this analysis.*

Table 2 summarizes the mean cognitive test scores in Tromsø6 and Tromsø7 (subsample with repeated measurement) by smoking status stratified by AF. Age, sex, and education covariates were adjusted during this analysis.

Verbal memory test:

In Tromsø6 never smoker without AF had the highest mean cognitive score which was 6.57 (95% CI 6.4, 6.6) and was increased to 7.02 (95% CI 6.91, 7.13) in Tromsø7. Among those with AF, in Tromsø6 current smoker had least mean cognitive score which was 5.23 (95% CI 4.6, 5.7) and 5.64 (95% CI 5.06, 6.21) in Tromsø7. Mean cognitive score was higher in every smoking group from Tromsø 6 to Tromsø7 (subsample with repeated measurement)

Digit symbol coding test:

Never smoker without AF group in Tromsø6 had the highest cognitive mean score which was 39.49 (95% CI 39.0, 39.9) and increased to 40.49 (95% CI 39.76, 41.23) in Tromsø7. The result showed that there was significant association between cognitive function and smoking in no AF group: - (p-value = 0.022 and 0.033 for Tromsø6 and Tromsø7 respectively.) Current smoker with AF had least cognitive score which was 26.44 (95% CI 22.9, 29.69) in Tromsø6 and 29.69 (95% CI 26.68, 32.69) in Tromsø 7.

Mini-mental state examination:

This test suggested that cognitive score was greater among the never smoker group without AF which is 28.18 (95% CI 28.04, 28.25) in Tromsø 6 and among current smoke which was 27.72 (95% CI 27.56, 27.89 CI) in Tromsø 7. Among respondents with AF, cognitive score was greater among current smoker in Tromsø 6 and in never smoker group in Tromsø 7. The association was not significant.

Tapping test:

Never smoker group without AF had the highest cognitive score in Tromsø6 which was 52.57 (95% CI 52.13, 53.01) in Tromsø6 and same group in Tromsø7 had highest score which was 55.11 (95% CI 55.11, 55.55). Smoking was significantly associated with cognitive function among those without AF in tapping test ($p < 0.001$) for both Tromsø6 and Tromsø7 with repeated measurement. Among those with AF, current smokers had the lowest cognitive score which was 44 (95% CI 40.29, 47.70) in Tromsø6 and previous smoker had least cognitive score which was 51.69 (95% CI 50.39, 52.98) in Tromsø7. However, the association was not significant.

In a nutshell, we can see that the mean cognitive score was higher in Tromsø7 (subsample with repeated measurement) compared toTromsø6. Cognitive function was higher among never smoker group without AF as shown by all 4 cognitive tests. As shown by digit-symbol coding test and tapping test smoking is significantly associated with cognitive function among those without AF and among those with AF the association was significant as shown by digit-symbol coding test in Tromsø6.

Table 3: Mean (95% CI) change in cognitive test scores over 6 years according to smoking status stratified by Atrial Fibrillation status (The Tromsø study)

	Change in test scores					
	Model I		**Model 2**		**Model 3**	
	Mean (CI)	**p-value**	**Mean (CI)**	**p-value**	**Mean (CI)**	**p-value**
Verbal memory test						
AF(No)						
Smoking						
Never	-0.126 (-0.283, 0.030)	0.299	-0.140 (-0.338, -0.058)	0.210	-0.229 (-0.483, 0.026)	0.323
Ever	-0.193 (-0.343, -0.043)		-0.077 (-0.298, 0.144)		-0.297 (-0.537, -0.057)	
AF (Yes)						
Smoking						
Never	-0.174(-0.601, 0.254)	0.710	-0.276 (-0.916, -0.364)	0.917	-0.293 (-1.027, 0.440)	0.996
Ever	-0.251(-0.631, -0.129)		-0.300 (-0.864, 0.264)		-0.294 (-0.963, 0.374)	
Digit-symbol coding test						
AF (No)						
Smoking						
Never	-4.408 (-5.429, -3.386)	0.019	-3.629 (-4.960, -2.298)	0.009	-3.506 (-5.225, -1.786)	0.018
Ever	-5.364 (-6.350, -4.371)		-4.792 (-6.081, -3.502)		-4.577 (-6.216, -2.937)	
AF (Yes)						
Smoking						
Never	-4.049 (-5.951, -2.147)	0.450	-5.746 (-8.430, -3.152)	0.202	-5.294 (-8.218, -2.370)	0.397
Ever	-3.377 (-5.073, -1.682)		-4.558 (-6.869, -2.246)		-4.494 (-7.161, -1.826)	
Mini-mental state examination						
AF (No)						
Smoking						
Never	-0.675 (-0.886, -0.463)	0.476	-0.755 (-1.013, -0.498)	0.295	-0.726 (-1.066, -0.387)	0.281
Ever	-0.619 (-0.827, -0.411)		-0.669 (-0.919, -0.419)		-0.636 (-0.963, -0.310)	
AF (Yes)						
Smoking						
Never	-0.354 (-1.124, -0.415)	0.827	-0.997 (-2.024, 0.030)	0.835	-1.519 (-2.731, -0.306)	0.704
Ever	-0.423 (-1.121, 0.275)		-0.927 (-1.865, 0.010)		-1.391 (-2.516, -0.265)	
Tapping test						
AF (No)						
Smoking						
Never	0.259 (-0.278, 0.797)	0.002	-0.050 (-0.730, 0.631)	0.002	-0.452 (-1.311, 0.408)	0.004
Ever	-0.405 (-0.923, 0.113)		-0.767 (-1.421, -0.114)		-1.110 (-1.925, -0.296)	
AF (Yes)						
Smoking						
Never	0.645 (-1.188, 2.478)	0.575	-0.058 (-2.684, 2.568)	0.549	-0.286 (-3.266, 2.694)	0.632
Ever	0.161 (-1.515, 1.837)		-0.632 (-3.077, 1.814)		-0.755 (-3.602, 2.092)	

Model 1 Adjusted with age, sex, education, and baseline test score Model 2: Model 1+ Total HDL Cholesterol ratio, physical activity, hypertension, BMI, and alcohol Model 3: Model 2+ myocardial infarction and HbA1c

Table 3 shows adjusted mean change in cognitive score by smoking status stratified by AF status. Smoking was significantly associated with cognitive decline as shown by digit-symbol coding test and tapping test among those without AF. Although it is not statistically significant, cognitive decline is greater among the ever smoker group than never smoker group as shown by verbal memory test and tapping test.

After adjusting socio-demographic variables like age, sex, education, and baseline test score (model 1), cognitive decline was greater among ever smoker group in both groups with and without AF as measured by the verbal memory test. As measured by digit-symbol coding test, cognitive decline was greater among ever smoker group among those without AF [Mean = -5.36, 95% CI = -6.35, -4.37]. Also as measured by tapping test cognitive decline was greater among ever smoker group without AF [Mean = -0.405, 95% CI = -0.923, 0.113]. Cognitive decline is significantly associated with smoking as shown by digit-symbol coding test and tapping test among people without AF (p-value = 0.019 and 0.002 respectively).

We added some lifestyle and health measurement related variables such as total HDL cholesterol ratio, hypertension, physical activity, BMI, alcohol with model 1 (Model 2) for further adjustment to see the association. As measured by tapping test cognitive decline was higher among ever smoker group in both with and without AF respondents. Cognitive decline was significantly associated with smoking among respondents without AF as shown by digit-symbol coding test and tapping test with (P-value = 0.009 and 0.002) respectively. Verbal memory test showed that cognitive decline was higher among ever smoker group with AF.

We further added heart related disease myocardial infarction and HbA1c to the model 2 (model 3) for further adjustment to check the association. After this adjustment cognitive decline was found higher among ever smoker group with AF as measured by verbal memory test [Mean = -0.294, 95% CI = -0.963, 0.374] and ever smoker group without AF as measured by tapping test [Mean = -1.110, 95% CI = -1.925, -0.296]. Cognitive decline was significantly associated with smoking among respondents without AF as shown by digit-symbol coding test and tapping test (P-value = 0.018 and 0.004 respectively). After final adjustments (model 3) there was slightly higher cognitive decline as shown by tapping test, but slightly lower cognitive decline as shown by digit-symbol coding test among those without AF.

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CHAPTER IV: DISCUSSION

4.1 Summary of the findings

This longitudinal study investigated the association between smoking and cognitive function stratified by AF status among people who participated in the Tromsø6 and Tromsø7 study. Cognitive function was found to be improved in Tromsø and there was decline in smoking habit (figure 4 and 5). Smoking was significantly associated with AF in Tromsø6 (p-value <0.001) (Table 1). Cognitive score was greater among the never smoker without AF groups of Tromsø7 with repeated measurement than Tromsø6 (Table 2). As shown by digit-symbol coding test and tapping test smoking was significantly associated with cognitive function among those without AF and among those with AF the association was significant as shown by digit-symbol coding test in Tromsø6 (Table 2). After adjusting for the covariates (model 1, 2 and 3) the result showed that smoking was significantly associated with cognitive decline as shown by digit-symbol coding test and tapping test among those without AF (Table 3). However, the association was not significant among those with AF. Among non-smokers the mean cognitive decline was higher among those with AF compared to those without AF.

4.2 Cognitive function and smoking status in Tromsø

This study has showed that cognitive function has increased from Tromsø6 to Tromsø7 participants. We also found that there was reduced smoking prevalence and large number of participants had quit smoking. This finding was supported by Johnsen et al. which showed increased cognitive test scores in later-born birth cohorts in Tromsø. The main reason behind this was decreasing prevalence of smoking, increased education level, and physical activity among Tromsø inhabitants (12).

4.3 Smoking and cognitive decline association among those without AF.

Our study has clearly identified the significant association between smoking and cognitive decline among those without AF as measured by digit-symbol coding test and tapping test. To our best knowledge, there are not any studies which have investigated the association between smoking and cognitive decline stratified by AF status. However, there are many studies which have shown the association between smoking and cognitive decline among general population (5, 6, 8, 20, 24-27).

According to a meta-analysis, current smokers were at 1.27 times higher risk of any dementia than never smokers. Current smokers were at 1.30 times higher risk of dementia than former smokers (6). These findings are in line with our findings.

Out of 28 studies considered in one systematic review by Peter et al. seven studies found a significant link between smoking and increased risk of cognitive decline. This study concluded that there was 1.20 times higher chance of cognitive decline among current smokers than never or non-smokers (27). This finding is consistent with the result of our study which showed that cognitive decline is greater among the ever smoker group.

The Whitehall II cohort study had analyzed the association between cognitive function and smoking habit. This study had categorized smoker into current smokers, recent smokers, long term-smokers, never smokers. Cognitive function was measured in terms of global cognition, memory, vocabulary, executive function. This study concluded that the never smoking men had faster decline in global cognition -0.12 (95% CI, -0.19, -0.01 CI), memory -0.15 (95% CI, -0.29, -0.01), and executive function -0.11 (95% CI, -0.20, -0.03) (24). These findings match with our result.

A British cohort study investigated the association between smoking and cognitive function in mid-life among the British 1946 birth cohort adjusting socio-economic status and health indicators. This study concluded cigarette smoking was associated with faster declines in verbal memory between ages 43 and 53 years (26). These findings are consistent with our study result.

In our study, even after the adjustment of different covariates (model 1, 2 and 3) for cognitive decline the association remained significant between smoking and cognitive decline among those without AF as measured by tapping test and digit-symbol coding test. When adjusted with demographic variables such as age, sex, education, baseline cognitive score and health related behaviors and measurement such as total HDL cholesterol ratio, BMI, physical activity, alcohol the association between smoking and cognitive decline was still significant as shown by digit-symbol coding test and tapping test. These findings and adjustments of the variables were consistent to one of the similar studies conducted in Taiwan (33).

Tapping test and digit-symbol coding test have demonstrated the significant association between smoking and cognitive decline among people without AF in our study. Tapping test is important for cognition because reduced motor speed is a sensitive marker of motor and cognitive cerebral dysfunction which included reduced manual dexterity, coordination, and

global performance (34). Another study found that finger tapping demonstrated motor slowing preceded cognitive impairment (35).

The potential mechanism of smoking causing cognitive decline and dementia is well documented (4, 36). Smoking causes reduction of oxidants and free radical species which leads to oxidative stress. Senile plaque and neurofibrillary tangles are formed by increased oxidative stress, and this lead to cognitive decline, dementia (36).

4.4 Smoking and cognitive decline among those with AF:

Our study did not find any significant association between smoking and cognitive decline among the respondents with AF. However, mean cognitive decline was greater among ever smoker group as shown by verbal memory test and tapping test. One large cohort study with 126,252 participants conducted in Korea concluded that all types of smoking status were associated with risk of dementia in patients with newly diagnosed AF (37). The findings from this study are inconsistent with our result. The result may have deviated because our study comprises of only never and ever smoker group. Those who quit smoking are also included in ever smoker group in our study. In contrast this Korean study has divided the smokers into never smoker, ex-smoker, quit smoker, current smoker group. This same study also demonstrated that cognitive function improved among those who quit smoking and had newly diagnosed AF. However, in our study those who quit smoking are in the same group as current smoker as ever smoker. Moreover, respondents of our study who had AF may have received recommendations from doctor to quit smoking, but they will still be in the ever- smoking group. We have seen from our result that many current smokers have quit smoking between Tromsø6 and Tromsø7. Another reason could be that along with quitting smoking, good diet, and increased physical activity improves the cognitive function and may be those with AF may have incorporated it in their daily life and might have had positive result in cognitive function. Therefore, the results of our study and Korean study may have been different.

More comprehensive research to find out the association between smoking cessation and cognitive decline among those with AF is required. One meta-analysis published in 2007 compared the cognitive function association between ever smoker group and never smoker group among the general population. This study showed there was no cognitive decline for ever smoking group compared with never smoking (6). This result is consistent with our findings.

4.5 Limitations

Our result was based on the hospital diagnosis registry which means undiagnosed (silent AF), cases of AF were not assessed by this study. This might have led to underestimation of AF cases. Similarly, other covariates like smoking, alcohol, physical activity, MI were assessed through self-administered questionnaire. Certain habits such as physical activity tend to be overreported and certain habits such as alcohol use, smoking etc. tend to be underreported. This may have led to misclassification bias. Selection bias might have occurred as people with cognitive impairment and dementia might have participated less in number in the Tromsø Study. Participants with repeated cognitive testing were younger and had better risk profile compared to those loss to follow-up.

4.6 Strength:

This is a longitudinal study and includes follow-up of a large cohort with repeated sensitive cognitive test over the period of 9 years. Repeated sensitive cognitive test were performed in both Tromsø studies. The participants in this study had high attendance rate and included both sexes. Thorough case validation of AF cases was another strength.

CHAPTER V: CONCLUSION

Smoking is significantly associated with cognitive decline among people without AF as measured by digit-symbol coding test and tapping test. Although the association was not statistically significant, cognitive decline was somewhat greater among the ever smoker group than never smoker group as measured by verbal memory test and tapping test in both groups with and without AF. We did not find any significant association between smoking and cognitive decline among those with AF. However, in the future a larger study with enough power to categorize smoking groups including quitters as separate group among those with AF is required to explore a possibly true association.

CHAPTER VI: RECOMMENDATION

Public health workers should give recommendations to quit smoking as it affects the cognitive function for both people with and without AF.

REFERENCES:

1. World Health Organization. Tobacco 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/tobacco.
2. World Health Organization. Tobacco/Data and statistics 2022 [Available from: https://www.euro.who.int/en/health-topics/disease-prevention/tobacco/data-and-statistics.
3. Statistics Norway. Tobacco, alcohol and other drugs 2021 [Available from: https://www.ssb.no/en/helse/helseforhold-og-levevaner/statistikk/royk-alkohol-og-andre-rusmidler.
4. Chang RC-C, Ho Y-S, Wong S, Gentleman SM, Ng H-K. Neuropathology of cigarette smoking. Acta neuropathologica. 2014;127(1):53-69.
5. Amini R, Sahli M, Ganai S. Cigarette smoking and cognitive function among older adults living in the community. Aging, Neuropsychology, and Cognition. 2021;28(4):616-31.
6. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. American journal of epidemiology. 2007;166(4):367-78.
7. Arntzen K, Schirmer H, Wilsgaard T, Mathiesen E. Impact of cardiovascular risk factors on cognitive function: the Tromsø study. European journal of neurology. 2011;18(5):737-43.
8. Xiong N, Shen J, Wu B, Yan P, Shi H, Li J, et al. Factors influencing cognitive function in patients with atrial fibrillation: a cross-sectional clinical study. Journal of International Medical Research. 2019;47(12):6041-52.
9. Nations U. Peace, Dignity and Equality on a healthy planet 2022 [03/04/2022]. Available from: https://www.un.org/en/global-issues/ageing.
10. ICD-10. International Statistical Classficiation of Diseases and Related Health Problems 10th revision (ICD-10) version for 2010 [Available from: https://icd.who.int/browse10/2010/en#/F06.7.
11. Pais R, Ruano L, P Carvalho O, Barros H. Global cognitive impairment prevalence and incidence in community dwelling older adults—a systematic review. Geriatrics. 2020;5(4):84.
12. Johnsen B, Strand BH, Martinaityte I, Mathiesen EB, Schirmer H. Improved Cognitive Function in the Tromsø Study in Norway From 2001 to 2016. Neurology: Clinical Practice. 2021;11(6):e856-e66.
13. Blom K, Emmelot-Vonk MH, Koek HDL. The influence of vascular risk factors on cognitive decline in patients with dementia: a systematic review. Maturitas. 2013;76(2):113-7.
14. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European heart journal. 2021;42(5):373-498.
15. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nature Reviews Cardiology. 2014;11(11):639-54.
16. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clinical epidemiology. 2014;6:213.
17. Kjerpeseth LJ, Igland J, Selmer R, Ellekjær H, Tveit A, Berge T, et al. Prevalence and incidence rates of atrial fibrillation in Norway 2004–2014. Heart. 2021;107(3):201-7.
18. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. Circulation. 2017;136(6):583-96.

19. Nishtala A, Piers RJ, Himali JJ, Beiser AS, Davis-Plourde KL, Saczynski JS, et al. Atrial fibrillation and cognitive decline in the Framingham Heart Study. Heart Rhythm. 2018;15(2):166-72.
20. Tiwari S. Atrial Fibrillation: A prospective population study of risk factors and complications. The Tromsø Study. 2018.
21. Tiwari S, Løchen M-L, Jacobsen BK, Hopstock LA, Nyrnes A, Njølstad I, et al. Atrial fibrillation is associated with cognitive decline in stroke-free subjects: the Tromsø Study. European journal of neurology. 2017;24(12):1485-92.
22. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Annals of internal medicine. 2013;158(5_Part_1):338-46.
23. Ding M, Qiu C. Atrial fibrillation, cognitive decline, and dementia: an epidemiologic review. Current Epidemiology Reports. 2018;5(3):252-61.
24. Sabia S, Elbaz A, Dugravot A, Head J, Shipley M, Hagger-Johnson G, et al. Impact of smoking on cognitive decline in early old age: the Whitehall II cohort study. Archives of general psychiatry. 2012;69(6):627-35.
25. Nooyens AC, van Gelder BM, Verschuren WM. Smoking and cognitive decline among middle-aged men and women: the Doetinchem Cohort Study. American journal of public health. 2008;98(12):2244-50.
26. Richards M, Jarvis MJ, Thompson N, Wadsworth ME. Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. American journal of public health. 2003;93(6):994-8.
27. Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC geriatrics. 2008;8(1):1-7.
28. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the Tromsø study. International journal of epidemiology. 2012;41(4):961-7.
29. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njølstad I. The sixth survey of the Tromsø study (Tromsø 6) in 2007–08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scandinavian journal of public health. 2013;41(1):65-80.
30. Hopstock LA, Grimsgaard S, Johansen H, Kanstad K, Wilsgaard T, Eggen AE. The seventh survey of the Tromsø Study (Tromsø7) 2015–2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. Scandinavian Journal of Public Health. 2022:14034948221092294.
31. Organization WH. AUDIT: The alcohol use disorders identification test: Guidelines for use in primary health care. World Health Organization; 2001.
32. Ruiz PL-D, Hopstock LA, Eggen AE, Njølstad I, Grimnes G, Stene LC, et al. Undiagnosed diabetes based on HbA1c by socioeconomic status and healthcare consumption in the Tromsø Study 1994–2016. BMJ Open Diabetes Research and Care. 2021;9(2):e002423.
33. Wang C-C, Lu T-H, Liao W-C, Yuan S-C, Kuo P-C, Chuang H-L, et al. Cigarette smoking and cognitive impairment: a 10-year cohort study in Taiwan. Archives of gerontology and geriatrics. 2010;51(2):143-8.
34. Desrosiers J, Bourbonnais D, Bravo G, Roy P-M, Guay M. Performance of the 'unaffected'upper extremity of elderly stroke patients. Stroke. 1996;27(9):1564-70.
35. Camicioli R, Howieson D, Oken B, Sexton G, Kaye J. Motor slowing precedes cognitive impairment in the oldest old. Neurology. 1998;50(5):1496-8.
36. Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. PloS one. 2015;10(3):e0118333.

37. Lee H-J, Lee S-R, Choi E-K, Park S-H, Chung J-W, Choi J-M, et al. Risk of Dementia After Smoking Cessation in Patients With Newly Diagnosed Atrial Fibrillation. JAMA network open. 2022;5(6):e2217132-e.