Student thesis

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Student thesis in Medicine
Supervisor: Geir Selbæk
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Abstract

Background: Even though smoking is considered a risk factor for dementia development, there is still uncertainty to the question. The objective of this study is to investigate the relationship between smoking as an independent risk factor and incidence of dementia.

Methods: This longitudinal cohort study was based on data from the Trøndelag Health Study (HUNT). The population consisted of 8,532 Norwegian men and women 47 years or older, who were followed-up for an average of 21.8 years. Information on smoking and covariates was extracted from HUNT2 (1995-97). Data on dementia outcome were obtained from a comprehensive standardized diagnostic assessment in HUNT4 70+ (2017-19). Poisson regression models were used to estimate risk ratios (RR) for the total population and for women and men separately, using never smokers as the reference category in all analyses. We performed several sensitivity analyses, including an analysis with accumulated smoking amount (pack-years) as exposure.

Results: Current smokers had a 31% higher dementia risk (RR 1.31, 95% confidence interval (CI) 1.12-1.52, p-value 0.000, n=8,532) compared to never smokers. Slightly stronger associations were found for women (RR 1.38, 95% CI 1.14-1.66, p-value 0.001, n=4,727). No association was found for men (RR 1.26, 95% CI 0.98-1.40, p-value 0.073, n= 3,805). No clear relationship was observed between former smoking and dementia. Pack-years was not significantly associated with dementia (RR 1.01, 95% CI 1.00-1.01, p-value 0.094, n=4,421).

Conclusion: In this cohort current smoking was associated with an increased risk of dementia. We found no association between former smoking and dementia risk. Our findings indicated that there is a difference in risk between female and male smokers, but this might be a biased result due to participants lost to death between baseline and follow-up.

Table of content

1 Introduction

Dementia has been defined in many ways. It can be described as any decline in cognition that is substantial enough to affect how a person functions in their daily life (1). The Diagnostic and Statistical Manual of Mental Disorders (DSM) V differentiates between mild and major neurocognitive disorders. DSM V criteria for major neurocognitive disorder, also known as dementia, includes the presence of a significant decline in one or more cognitive domains compared to a former level, which interferes with independence in activities of everyday life, does not only occur in a delirium and is not better explained by another mental disorder (1). Mild neurocognitive disorder, also known as mild cognitive impairment (MCI), can be defined as a substantial decline in cognition which exceeds changes that can be expected in normal aging, but has little or no impact on independence in daily life (2). This condition may or may not advance to dementia.

Dementia may be best described as a syndrome rather than a specific disease (3), as it can be caused by a variety of neurological and medical conditions that primarily or secondarily affect the brain (4). The cognitive deterioration is usually chronic or progressive and may include impairment in cognitive domains such as memory, learning, attention, visuospatial abilities, executive functions, and language, as well as behavioral and emotional changes. Common forms of dementia are Alzheimer's disease (AD), which may account for up to 70% of cases, vascular dementia (VaD), Lewy body dementia and frontotemporal dementia. Neurodegenerative dementia types are most prevalent in the elderly population, whereas traumatic brain injury and brain tumors are the most common causes in younger persons (3). Life expectancy after a diagnosis of AD is approximately 7-10 years for persons diagnosed in their sixties and early seventies (5). The survival time is even shorter for individuals diagnosed later in life. A systematic review and meta-analysis found that the mean survival time was 7.6 years after the onset of AD and 5.8 years after receiving a diagnosis of AD (6). Compared to this the mean survival time in other dementia types was approximately one year shorter. Studies indicate that neuropathological changes associated with AD can be detected up to a decade prior to overt symptoms of MCI and up to 20 years before manifest symptoms of AD (7).

Dementia is one of the key health care challenges for society, both nationally and internationally. It causes profound distress on the people affected, as well as their caregivers, and is a huge organizational and financial challenge for society. Over 55 million people live

with dementia worldwide. This number is rising every day with forecasts reaching 78 million by 2030 and 152.8 million by 2050 (8, 9). The total healthcare spending on patients with dementia has been estimated to 594 billion USD in 2019. This is expected to reach 1.6 trillion USD by 2050, with a possibility to reach as high as 2.4 trillion USD. It is projected to represent 11% of all expected health spending in 2050 (10). A Norwegian study from 2021 estimated that there were 101,118 persons with dementia in Norway in 2020, and that this is projected to increase to 236,789 and 380,134 in 2050 and 2100, respectively (11). These future projections indicate that dementia will cause further distress and greater challenges for generations to come.

In recent years there has been a huge increase in knowledge about disease mechanisms in various types of dementia. Results from research on curative and disease-modifying agents have been disappointing (12). There have been several attempts to develop a drug that uses antibodies to clear amyloid-beta (Aβ) from the brain. In June 2021 the United States Food and Drug Administration (FDA) approved Aduhelm (aducanumab), the first disease-modifying treatment for AD (13). This seemed promising for future treatment of AD. However, the U.S. agency acknowledged that there was not enough evidence to show that the drug has a clinical benefit, and in April 2022 the European Medicines Agency (EMA) recommended a refusal of the marketing authorization of Aduhelm (14). The latest contribution in the line of anti-Aβ antibodies is lecanemab, an antibody targeting larger Aβ oligomers. In a phase 3 trial it showed promising clinical benefit but was also associated with adverse events (15). While waiting for a potential treatment there has also been focus on other ways to reduce the prevalence of dementia. Even though the number of people with dementia increases, the age-specific incidence of dementia is decreasing (16). This has been attributed to changes in modifiable risk factors, such as education and cardiovascular diseases. In the 2017 *Lancet Commission on dementia prevention, treatment, and care* it was calculated that more than one third of dementia cases could be delayed or prevented by interventions directed at nine modifiable risk factors: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact (16). It has been estimated that delaying the onset of AD, the most common type of dementia, by five years will result in 41% lower prevalence and 40% lower cost of AD by 2050 (17).

In the 2020 *Lancet Commission on dementia prevention, treatment, and care* additional three modifiable risk factors have been identified along with the nine from 2017: excessive alcohol

consumption, traumatic brain injury, and air pollution. However, the timing of the risk exposure, and even the direction of the effect, is not fully clarified. Smoking was considered the potentially third most important modifiable risk factor according to calculated population attributable fractions (PAFs), with an estimated 5% dementia risk reduction in the population if smoking was eliminated (18). Despite this, the high PAF of smoking is much contributed to its high prevalence, and not to a strong cause-effect relationship. According to the global report on trends in prevalence of tobacco smoking by the World Health Organization (WHO), the prevalence is decreasing for both males and females in all WHO regions. Despite this, the number of tobacco smokers aged 15 years or older remains high, estimated to 1071 million in 2018, a prevalence of almost 18.9% among adults. Internationally there is a significant preponderance of male smokers compared to female smokers, with prevalences of 32.4% and 5.5%, respectively. In the Americas, European and Western Pacific regions smoker numbers are declining, while they are continuing to grow in the African, Eastern Mediterranean and South-East Asian regions (19). In Norway approximately 8% of the population between 16 and 74 years of age were daily smokers in 2021, which amounts to about 360,000 persons, while 8% smoked intermittently. In Norway, the difference in prevalence between women and men is not as pronounced as internationally, and there is a greater proportion of women than men who smoke. In 2021 approximately 9% of women and 6% of men were daily smokers (20). Smoking prevalence was considerably higher among persons over the age of 45.

Several studies have indicated that smokers have an increased risk of cognitive decline, AD, VaD and any dementia (21-24). Systematic reviews and meta-analyses have also found this association (25-28). The impact of exposure to second-hand smoke on dementia risk has also been studied. The evidence regarding this association is scarce, but a meta-analysis of cohort studies found a positive association between second-hand smoke and cognitive impairment (29), and one study indicated that passive smoking can lead to memory deterioration even after adjusting for other confounding factors (30). Contrarily, twenty to thirty years ago several studies reported that tobacco smoking was protective against dementia, and particularly AD. However, later reviews have found many epidemiological studies to be influenced by the tobacco industry. A systematic review of studies without tobacco industry affiliations found smoking to be associated with a 45% higher risk of dementia, whereas studies with tobacco industry affiliations reported a 40% lower risk of dementia (31). Cohort studies and case-control studies have also been shown to produce conflicting results. A meta-analysis comparing cohort studies with case-control studies found a risk ratio of 1.99 (95% CI

1.33-2.98) for the cohort studies and a pooled odds ratio of 0.82 (95% CI 0.53-1.27) for the case-control studies (32). This difference was mainly explained by weaknesses in the case-control study design, like survival bias.

Even though smoking is considered a risk factor for dementia, there is still uncertainty to the question. Some studies report that there is no association between smoking and the onset of dementia or AD (33, 34). A systematic review and meta-analysis from 2014 stated that current evidence from epidemiological studies on the effect of smoking exposure on cognitive outcomes was inconclusive (35). In a meta-analysis from 2020 on the hazards of smoking, AD and dementia were considered not sufficiently proven to be caused by smoking (36). Other studies find an increased risk of AD, but not a significantly increased risk of VaD, dementia unspecified or cognitive decline (26). A meta-analysis of modifiable risk factors for AD found that current smoking renders protection from AD in the Western population, while it increases risk in the Asian population (37). Even in studies which conclude that there is an association between current smoking and increased risk of dementia, cognitive decline, AD and/or VaD, one often fails to find a clear association between former smoking and increased dementia risk (25-27). Previous studies also indicate that there may be little difference in dementia risk between persons who have smoked lightly or intermittently and persons who have never smoked (23).

The pathophysiology explaining the association between smoking and dementia is yet to be established, but several mechanisms have been suggested. Mechanisms explaining the effect include neurotoxicity due to oxidative stress, inflammation, and atherosclerosis (38, 39). The link between smoking and cardiovascular impairment is considered a plausible mechanism in the development of AD and VaD. There are also additional mediating factors except cardiovascular disease that might contribute to the association between smoking and cognitive impairment. Smoking is considered a risk factor for diabetes, hearing impairment, hypertension, and dyslipidemia (40-44). There have also been studies linking smoking to physical inactivity, sleep-related issues, loneliness, and depression (45-48). It is well known that smoking prevalence is higher among less educated persons and manual workers (20). These are all factors associated with higher dementia risk (18, 49-53). Twenty to thirty years ago when several studies indicated that smoking was protective against dementia, the believed explanation was linked to the nicotine receptor. The number of nicotinic receptors is reduced in both AD and Parkinson’s disease, and the explanation was that nicotine increased the

density of nicotinic receptors in the brain, thus postponing the onset of disease (54). Even though evidence points in the direction that smoking is harmful to cognitive health, there is still a plausible mechanism that nicotine itself is beneficial in dementia and AD in particular (55).

2 Objectives

Our objective is to investigate the relationship between smoking and incidence of dementia. By adjusting for most known confounders we want to investigate the independent effect smoking has on dementia risk.

3 Material and methods

This longitudinal cohort study was based on data from the four waves of the Trøndelag Health Study (HUNT), with a large and representative population, adjustment for most known confounders, with a long follow up, and a standardized diagnostic assessment of dementia.

In our main analysis we investigated the relationship between smoking and dementia according to smoking status at baseline. Smoking status was divided into three categories: current, former, and never smoker. We investigated the relationship for women and men aged 70 years and older with known smoking status from HUNT2 and cognitive test results in HUNT 70+. We performed an additional sensitivity analysis to investigate the relationship between accumulated smoking amount and dementia. Accumulated smoking amount was measured in pack-years.

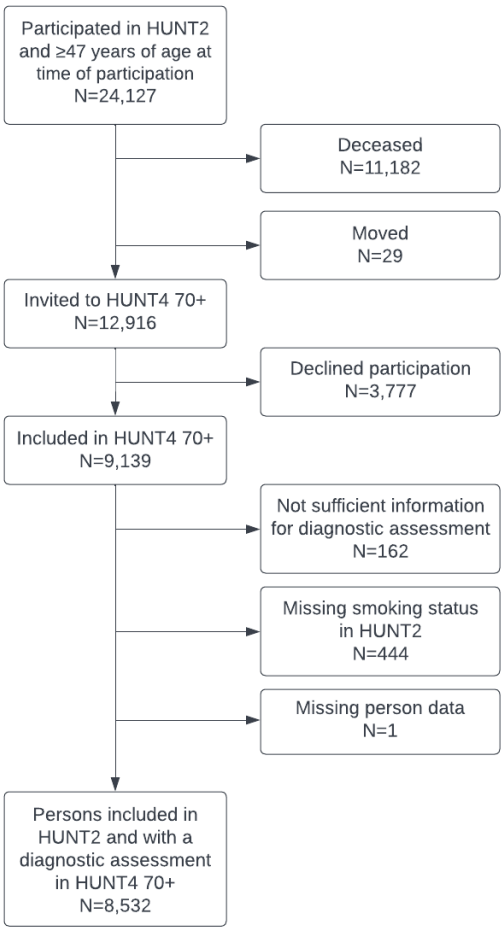
3.1 Study population

The HUNT study is an ongoing population-based cohort study that has collected comprehensive data on participants' health and lifestyle through questionnaires, interviews, and clinical measurements. All inhabitants aged 20 years or older in the northern part of Trøndelag in Norway are invited to establish the population cohorts. The area consists of small towns of less than 25,000 inhabitants and rural areas. Compared to the rest of the country there are proportionately fewer immigrants and fewer highly educated persons in this area, while general health, cause-specific mortality, disability insurance, and unemployment rate are comparable to the national average (11). A total of four surveys (HUNT1-4) has been

completed over a period of 35 years (56). HUNT1 took place in 1984-86 and included 77,212 (89.4% of invited) participants; HUNT2 in 1995-97 with 65,237 (69.5%) participants; HUNT3 in 2006-08 with 50,807 (54.1%) participants and HUNT4 in 2017-19 with 56,042 (54.0%) participants (57, 58). Participation rates in the older age groups (50+ years) were considerably higher. In HUNT4 all individuals aged 70 years and older were invited to participate in the HUNT4 70+ study. This study included 19,403 (51.2%) persons and assessed participants using questionnaires, clinical measurements, biological samples, cognitive tests, interview with next of kin, and assessment of functional capacity (11).

Our study cohort includes individuals from HUNT2 that were or would have been 70 years or older at the time of participation in HUNT4 70+ (N=24,127), and that also participated in HUNT4 70+ (N=9,139). Our analytic cohort comprises 8,532 people. Participants that had missing data on the smoking questionnaire or did not have sufficient information for setting a dementia diagnosis were excluded (Figure 1).

Figure 1: Flow chart of the study population.



3.2 Variables

3.2.1 Dementia

The main outcome was defined as all-cause dementia. Data on dementia diagnosis were extracted from the HUNT4 70+ study. Participants were evaluated through cognitive tests which were performed by trained healthcare workers. Based on each participant's preference, testing took place at a field station or at their home or nursing home. The test battery included the Montreal Cognitive Assessment (MoCA) scale, the World List Memory Task for participants with a MoCA score (≥22) that indicated a higher cognitive function and who could recall at least one of the five words in the MoCA delayed recall test, and the Severe Impairment Battery-8 for participants who were assessed to have moderate or severe dementia (11, 59). It also included the Instrumental Activities in Daily Living Scale, the Physical Self-Maintenance Scale, the Neuropsychiatric Inventory Questionnaire, the Clinical Dementia Rating Scale, and the Hospital Anxiety and Depression Scale (HADS). Participants were questioned about core symptoms, the debut and course of symptoms, subjective cognitive decline, family history of dementia and previous dementia assessment and diagnosis. Interview with next of kin was performed in cases where dementia was suspected to be present. A final diagnosis was made by a working group of nine clinical experts in geriatrics, neurology or old-age psychiatry based on the DSM V criteria. An independent diagnosis was made by two experts for each participant. If no consensus was reached after comparing the diagnoses, a third expert was consulted. The working group had access to all the available data. Participants were classified into four different groups of cognitive function: no cognitive impairment, amnestic MCI, non-amnestic MCI, or dementia. Those who received a dementia diagnosis were further categorized into dementia subtypes based on clinical symptoms and additional information from next of kin on the development of symptoms. Further details on diagnostic procedures in the HUNT4 70+ study can be found in the article by Gjøra et al. from 2021 (11).

3.2.2 Smoking

Exposure was assessed using data on smoking status from HUNT2 and pack-years from HUNT4. Information was collected 18-23 years prior to cognitive testing in HUNT4 70+. Participants completed a self-reporting questionnaire about their current and former smoking habits, i.e. duration, frequency, and amount of smoking. Based on the reported answers HUNT constructed a smoking status variable and a pack-year variable.

Smoking status

In HUNT2 participants were asked “Do you smoke?” and gave answers regarding whether they smoked cigarettes daily, cigar/cigarillos daily and/or pipe daily or if they never smoked daily. Based on the responses they were classified as either “current smoker daily”, “ex-smoker daily” or “never smoked daily”. The variable was corrected regarding answers reported in HUNT1 and HUNT3 (60). In HUNT2 participants were asked about daily and not occasional smoking. As indicated previously, there may be little difference in risk of dementia development between light and occasional smokers and never smokers.

Pack-years

To assess whether there may be a dose dependent relationship between smoking and the risk of dementia, we performed a sensitivity analysis with pack-years as exposure. Several studies suggest that dementia risk increases with smoking intensity and duration (22-24, 27, 61, 62). In HUNT1-4 participants were asked how many cigarettes they smoked daily and how many years in total they have smoked daily. Pack-years were calculated by multiplying the number of cigarette packs per day (where one pack equals 20 cigarettes) with the number of years of daily smoking. In our analysis we included pack-years calculated in HUNT4. If pack-years from a previous survey was available, the most recent value was used, and any contribution from the HUNT4 study was added (63). The formula did not compensate for inconsistent base variables.

3.2.3 Covariates

Directed acyclic graphs, together with a priori knowledge and clinical judgements, were used to map the causal association between the variables. All baseline variables except for education were obtained from the HUNT2 study. Measurements of weight, height and blood pressure (BP) were performed by trained health professionals at examination stations. Information about education, marital status, alcohol consumption, psychological distress, diabetes, hearing loss, apoplexia, sleep disturbance, ischemic heart disease (IHD), physical activity (PA) and traumatic brain injury (TBI) was collected from self-report questionnaires. In addition, blood analyses of HbA1c were used to define diabetes. Information about cholesterol was solely based on blood samples. Beside age and sex, the following covariates are part of analyses in this project.

Education

We gathered information on educational background from HUNT1, and from HUNT2-4 if missing from HUNT1. It is likely that the participants would recall their education more

correctly at a younger age. HUNT1 participants were asked the following question: “What is your educational background? Only specify highest level achieved.”. The answering options were: “7 years primary school or less”, “Middle school”, “9 years compulsory primary or lower secondary school”, “10 years primary or lower secondary school”, “One or two years at upper secondary school”, “General certificate of education, commercial college or sixth form college”, “College or university, less than 4 years” or “College or university, 4 years or more”. In HUNT2-4 participants were asked the following question: “What is your highest level of education?”. Answering options in HUNT2 were: “Primary school 7-10 years, continuation school, folk high school”, “High school, intermediate school, vocational school, 1-2 years high school”, “University qualifying examination, junior college, A levels”, “University or other post-secondary education, less than 4 years” and “University/college, 4 years or more”. In HUNT3 answering options were: “Compulsory primary and lower secondary school”, “Vocational / upper secondary school”, “General education or sixth form of comprehensive school”, “College or university less than 4 years” and “College or university, 4 years or more”. In HUNT4 answering options were: “9-10 years compulsory primary and lower secondary school”, “One or two years of academic or vocational school”, “3 years of academic or vocational school”, “3-4 years vocational school/apprentice (upper secondary/sixth form college)”, “College or university less than 4 years” and “College or university, four years or more”. Educational level was divided into three categories based on the Norwegian Standard Classification of Education (64): compulsory (0-10 years), intermediate (11-14 years) and higher education (>14 years), and included as an ordinal variable.

Marital status

Participants stated their marital status based on five possible variable choices: “married”, “unmarried”, “widow/widower”, “divorced” and “separated”. From this we constructed two categories. Answering one of the latter four was categorized as being “unmarried”, the second category was “married”. Marital status was included as a dichotomous variable.

Alcohol consumption

Alcohol consumption was measured as total alcohol units per week. One unit of alcohol in Norway is equal to 33 cl beer (4.5% alcohol), 15 cl wine (12% alcohol) or 4 cl spirits (40% alcohol). A calculation of total units per week was made by combining five variables from the self-report questionnaire. The participants were asked «concerning alcohol, are you a non-drinker?», with a possibility to answer «Yes» or «No», and total units per week was set as 0 if

the answer to this question was yes. Participants were also asked «How many times a month do you normally drink alcohol» and «How many glasses of beer, wine or spirits do you usually drink in the course of two weeks? Put 0 if you don't drink alcohol.». Participants then gave separate answers for the number of glasses of beer, glasses of wine and glasses of spirits. Participants were asked not to count light beer. Answers given as zero (0) were set as missing if the participant had reported usually drinking >1 times a month (65). Missing was set as value 0, if the participant reported No to total abstinence and reported usually not drinking monthly (value 0) in the baseline questionnaire or in the additional HUNT2 lung study. Alcohol consumption was included as an ordinal variable separated into five categories: 0 units/week, 1-10 units/week, 11-20 units/week, 21-30 units per week and >30 units per week.

Psychological distress

Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). HADS can be divided into an anxiety score (HADS-A) and a depression score (HADS-D), with seven questions belonging to each of the scores. All items are scored on a 4-point scale ranging from 0 to 3. Scores are categorized as normal (<8), mild (8-10), moderate (11-14), and severe (15-21). Validation studies have found that HADS performs well as a screening tool to identify anxiety disorders and depression (66, 67). The Norwegian translation has demonstrated acceptable internal consistency with Cronbach's alpha scores 0.70 or higher (68, 69). Studies find a high sensitivity and specificity for scores ≥ 8 for both subscales (67, 70). In HUNT2 the question regarding "feeling tense or wound up" is missing from the HADS-A. Consequently, our scale only consisted of thirteen questions. In our regression model, HADS-total was included as a continuous sum score.

Body mass index

Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Weight and height were measured with the participants wearing light clothes without shoes. Weight was measured to the nearest half kilogram and height to the nearest centimeter. We included BMI as a continuous variable measured in kg/m^2.

Diabetes

In participants who attended additional examinations in HUNT2, measurement of HbA1c was available. If participants had a HbA1c ≥48 mmol/mol they were defined as having diabetes. If measurement of HbA1c was not available participants were defined as having diabetes if they answered «yes» to the question «Have you had or do you have diabetes?». The self-reported

diabetes diagnoses in HUNT have been validated by comparing answers with medical records (71). If missing, logical imputation with negative answers on the question «Have you had or do you have diabetes?» from later waves of HUNT was performed. Diabetes was included as a dichotomous variable.

Hypertension

BP was measured three times with 1-minute intervals using an automated oscillometric measuring device. The first measurement started after the participant was seated for two minutes, the arm resting on a table with the cuff on. We calculated mean systolic blood pressure (SBP) from the second and third measurements. If only two measurements were completed, the first and the second readings were used to calculate mean SBP. If missing, logical imputation with negative answers from current and later waves of HUNT was performed. Mean SBP was included as a continuous variable measured in mmHg.

Hearing loss

Participants were asked if they had any disability owing to hearing impairment. Answering options were «No», «Slight», «Moderate» and «Severe». Hearing loss was included as an ordinal variable.

Apoplexia

Participants were asked if they ever had a stroke/brain hemorrhage, response alternatives were «Yes» or «No». Apoplexia was included as a dichotomous variable.

Sleep disturbance

To assess sleep disturbance we used the question «Have you, during the last two weeks, felt bothered or distressed by anything listed below? - Difficulty falling asleep, staying asleep» with answering options “Not at all”, “A little”, “Quite a bit” and “Extremely”. If missing we used the question “During the last month, have you woken too early and not been able to get back to sleep?”. Answering options were «Never», «Now and again», «Often» and «Almost every night». Sleep disturbance was included as an ordinal variable.

Ischemic heart disease

Participants were asked if they ever had experienced a heart attack. Response alternatives were «Yes» or «No». If missing, logical imputation with negative answers from later waves of HUNT was performed. IHD was included as a dichotomous variable.

Physical activity

In HUNT2 participants were asked «How has your leisure-time physical activity been the last year? Think of a weekly average for the year. Your commute to work counts as leisure-time». Participants answered this question separately for light (no sweating or being out of breath) and hard (sweating and/or out of breath) PA. The answering options were «None», «Under 1», «1-2» or «3 or more», measured in hours. The validity of the HUNT2 questionnaire item on leisure-time PA has been examined (72). The question regarding hard PA was found to be reasonably valid as a measure for vigorous activity. Weaker or no correlations were observed for self-reported light PA. To estimate the metabolic equivalent (MET) hours per week we converted answers as follows: «None» = 0 h/week, «Under 1» = 0.5 h/week, «1-2» = 1.5 h/week and «3 or more» = 3.5 h/week. We multiplied hours per week light PA by 2,5 METs and hard PA by 7 METs, according to conventionally accepted intensity values (73). We included MET-h/week as a continuous variable.

Cholesterol

In our study cholesterol was assessed based on participants' level of high-density lipoprotein (HDL) cholesterol. Serum HDL cholesterol concentration was measured enzymatically in a non-fasting fresh blood sample. Our analysis included HDL cholesterol as a continuous variable measured in mmol/L.

Traumatic brain injury

Participants were asked if they had ever been hospitalized for a head injury. The response categories were "Yes, "No" or "Don't know, may be". TBI was defined as answering "Yes" and included as a dichotomous variable.

3.3 Methods

Baseline data on smoking status and covariates were collected 18-23 years prior to dementia assessment. Smoking status was divided into three categories: current, former and never smoker. In our main analysis we included 8,532 women and men aged 70 years and older with known smoking status at baseline and cognitive test results in HUNT4 70+. Never smokers were used as the reference category in all analyses when investigating the dementia risk among former and current smokers separately. The main analysis (Model B) calculates the association between smoking and all-cause dementia stratified by sex with adjustment for confounders: education, marital status, alcohol consumption and psychological distress, with multiple imputation (MI) imputed missing values. In sensitivity analyses we repeated this

procedure in two other models, but with adjustment for other factors. Model A was adjusted for age. Model C was adjusted for model B and additional covariates associated with exposure and/or outcome: BMI, diabetes, BP, hearing loss, PA, apoplexia, sleep disturbance, IHD and HDL cholesterol. We also included complete case analyses for model B. Finally, we performed an additional sensitivity analysis to investigate the relationship between accumulated smoking amount and dementia. Accumulated smoking amount was measured in pack-years up to the year of follow-up. In all analyses the association was investigated for the total population and for women and men separately. Dementia risk was estimated as risk ratios (RRs) with corresponding 95% confidence intervals (CI) and P-values of the differences between groups.

3.3.1 Missing data

Before multiple imputation, in the main analysis (Model B) 7,331 (85.9%) were complete cases (CC) with no missing data. Of all cases 1,088 (12.8%) had one missing, 110 (1.3%) had two missing, and three (0.0%) had three missing informations. The variables with missing were HADS (n=942, 0.11%), alcohol use (n=352), education (n=14), and marital status (n=9). When counting in other covariates used in sensitivity analyses (BMI, diabetes mellitus, BP, hearing impairment, stroke, sleep, PA, IHD, HDL cholesterol, and TBI) 534 (6.3%) were complete cases. Of these cases 7,740 had three or less missing informations.

3.3.2 Multiple imputation

Missing was first handled with logical imputation, then with MI. MI was performed using chained equation. All confounders and other covariates used in the analyses were included in the imputation procedure. In the imputation model linear regression or predictive mean matching (PMM) were performed for continuous variables, ordered logistic regression for ordinal variables and logistic regression for categorical and binary variables. To minimize bias, maximize use of available information, and obtain appropriate estimates of uncertainty we imputed 10 datasets before no further gain of additional datasets was achieved. As the variable HADS has numerous missing items, answers in three other tools for assessment of mental health in HUNT2 were included when performing MI. Those were the Symptom Check List 10, The Connor Mental Health Index, and The Four-Item Anxiety and Depression Index with questions overlapping the questions in HADS.

3.3.3 Statistical analysis

All analyses were performed with Stata/SE 17.0. Separate regression models were used to assess the association between smoking status and pack-years, and all-cause dementia. Because of significant interaction effects of smoking by sex, analyses were performed separately for men and women. Analyses of variance between the groups when exploring demographics were based on p-values found with one-way ANOVA for continuous variables, Kruskal-Wallis test for ordinal variables, and Pearson Chi square test for categorical variables. The association between smoking and dementia was analyzed using Poisson regression.

3.4 Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics Central Norway (REC central, Ref. No. 446916). A Data Protection Impact Assessment (DPIA) specific for this study was also performed and approved by the Norwegian Data Directorate.

The data collected in all the HUNT surveys has been approved by the Norwegian Data Directorate. All data is based on informed consent. In HUNT4, persons with reduced capacity to consent may also be included based on a proxy consent given by a close caregiver on behalf of the participant. This procedure was also approved by the ethics committee of HUNT and by the Regional Ethics Committee of Central Norway.

4 Results

4.1 Sociodemographic and clinical characteristics

There were 24,127 participants at baseline and 8,532 participants at follow-up. Mean follow-up time was 21.8 years (standard deviation (SD) 0.6), ranging from 18 to 23 years. From the 8,532 individuals at follow-up, 1,305 (15.3%) were diagnosed with dementia. The characteristics of the study population are summarized in Table 1. Mean age at baseline was 56.3, and age ranged from 47 to 82 years at time of inclusion in HUNT2. There was a higher proportion of women than men. The only group with a higher percentage of men than women was the former smoker group. The majority of the study population was married. The lowest percentage of married participants was found in the current smoker group. Current smokers tended to be younger, drink more, have a lower BMI, a lower BP, less diabetes and more

apoplexia compared to never smokers. Former smokers tended to be younger, drink more, have a higher BMI, more diabetes, more IHD and more apoplexia compared to never smokers.

Table 1. Baseline characteristics for the total sample and by categories of smoking status

	Total population	Current smokers	Former smokers	Never smokers	P-value	Missing
Sociodemographics						
N (%)	8,532 (100)	1,775 (20.8)	2,934 (34.4)	3,823 (44.8)		0
Women, N (%)	4,727 (55.4)	1,002 (56.5)	1,312 (44.7)	2,413 (63.1)	<0.001	0
Age, mean (range)	56.3 (47-82)	54.6 (47-79)	56.3 (47-82)	57.0 (47-82)	<0.001	0
Age group, N (%)					<0.001	0
46-50 y	2,485 (29.1)	666 (37.5)	862 (29.4)	957 (25.0)		
51-55 y	2,637 (30.9)	596 (33.6)	890 (30.3)	1,151 (30.1)		
56-60 y	1,621 (19.0)	273 (15.4)	546 (18.6)	802 (21.0)		
61-65 y	998 (11.7)	154 (8.7)	355 (12.1)	489 (12.8)		
66+ y	791 (9.3)	86 (4.8)	281 (9.6)	424 (11.1)		
Education, N (%)					<0.001	14
<10 y	5,022 (59)	1,148 (64.9)	1,710 (58.4)	2,164 (56.7)		
10-12 y	1,933 (22.7)	383 (21.6)	697 (23.8)	853 (22.3)		
>12 y	1,563 (18.4)	239 (13.5)	523 (17.9)	801 (21.0)		
Marital status, N (%)					<0.001	9
Unmarried	1,541 (18.1)	403 (22.7)	444 (15.1)	694 (18.2)		
Married	6,982 (81.9)	1,370 (77.3)	2,487 (84.9)	3,125 (81.8)		
Health and lifestyle						
Alcohol units/week, mean (SD)	1.6 (2.2)	2.0 (2.5)	2.0 (2.3)	1.2 (1.9)	<0.001	491
Pack-years, mean (SD)	15.8 (13.4)	23.9 (13.3)	11.5 (10.8)	1.1 (6.0)	<0.001	4,111
Comorbidity						
BMI, mean (SD)	26.8 (3.7)	25.8 (3.4)	27.4 (3.6)	26.9 (3.8)	<0.001	24
SBP, mean (SD)	138.8 (19.1)	134.5 (18.3)	139.2 (18.4)	140.0 (19.8)	<0.001	13
HDL cholesterol, mean (SD)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)	0.002	21
Diabetes, N (%)	133 (1.6)	13 (0.7)	68 (2.3)	52 (1.4)	<0.001	4
IHD, N (%)	152 (1.8)	27 (1.5)	84 (2.9)	41 (1.1)	<0.001	2
Apoplexia, N (%)	68 (0.8)	18 (1.0)	28 (1.0)	22 (0.6)	0.114	5

Abbrevations: N, number; y, years; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; HDL, high-density lipoprotein; IHD, ischemic heart disease. P-value of difference between groups.

4.2 Smoking and the risk of dementia

4.2.1 Current smokers compared to never smokers

In our main analysis (model B) current smokers had a 31% increased risk of dementia (RR 1.31, 95% CI 1.12-1.52, p-value 0.000, n=8,532) compared to never smokers (Table 2). Slightly stronger associations between current smokers and dementia were found for women. Women who currently smoked at baseline had a 38% increased risk of dementia (RR 1.38, 95% CI 1.14-1.66, p-value 0.001, n=4,727) compared with women who had never smoked at baseline (Table 2). We found no association between current smoking and dementia among men. Men who currently smoked at baseline had a RR of 1.26 (95% CI 0.98-1.61, p-value 0.073, n= 3,805) (Table 2). The analysis on complete cases shows similar results (Table 3).

4.2.2 Former smokers compared to never smokers

In our main analysis there was no association between former smoking and incident dementia. In the total population former smokers had a RR of 1.05 (95% CI 0.92-1.19, p-value 0.475, n=8532). Results also showed no association among women and men seperately, with RRs of 0.99 (95% CI 0.83-1.18, p-value 0.895, n=4,727) and 1.15 (95% CI 0.94-1.40, p-value 0.186, n=3,805), respectively. The analysis on complete cases shows similar results (Table 3).

Table 2: Association between smoking status and incident dementia in the main analysis

		No. Participants	No. Dementia cases	Model B, RR (95% CI) *P-value*
Total				
	Never smokers	3,823	604	1.00 (ref.)
	Former smokers	2,934	432	1.05 (0.92, 1.19) *0.475*
	Current smokers	1,775	269	1.31 (1.12, 1.52) *0.000*
Women				
	Never smokers	2,413	442	1.00 (ref.)
	Former smokers	1,312	177	0.99 (0.83, 1.18) *0.895*
	Current smokers	1,002	161	1.38 (1.14, 1.66) *0.001*
Men				
	Never smokers	1,410	162	1.00 (ref.)
	Former smokers	1,622	255	1.15 (0.94, 1.40) *0.186*
	Current smokers	773	108	1.26 (0.98, 1.61) *0.073*

Model B was adjusted for age + sex + confounders (education, marital status, alcohol consumption and psychological distress)

Table 3: Association between smoking status and incident dementia in the main analysis for complete cases

		No. Participants	No. Dementia cases	Model B, RR (95% CI) *P-value*
Total				
	Never smokers	3,269	463	1.00 (ref.)
	Former smokers	2,536	335	1.02 (0.88, 1.18) *0.790*
	Current smokers	1,526	206	1.28 (1.08, 1.52) *0.005*
Women				
	Never smokers	2,001	327	1.00 (ref.)
	Former smokers	1,116	125	0.89 (0.72, 1.10) *0.282*
	Current smokers	852	124	1.35 (1.08, 1.67) *0.008*
Men				
	Never smokers	1,268	136	1.00 (ref.)
	Former smokers	1,420	210	1.19 (0.96, 1.49) *0.119*
	Current smokers	674	82	1.24 (0.94, 1.64) *0.132*

Model B was adjusted for age + sex + confounders (education, marital status, alcohol consumption and psychological distress)

4.2.3 Sensitivity analyses

Smoking status

Among both current and former smokers, for the total population and for women and men seperately, results in model A and C were similar to the results in the main analysis. These are shown together with crude associations and model B in Table 4.

Pack-years

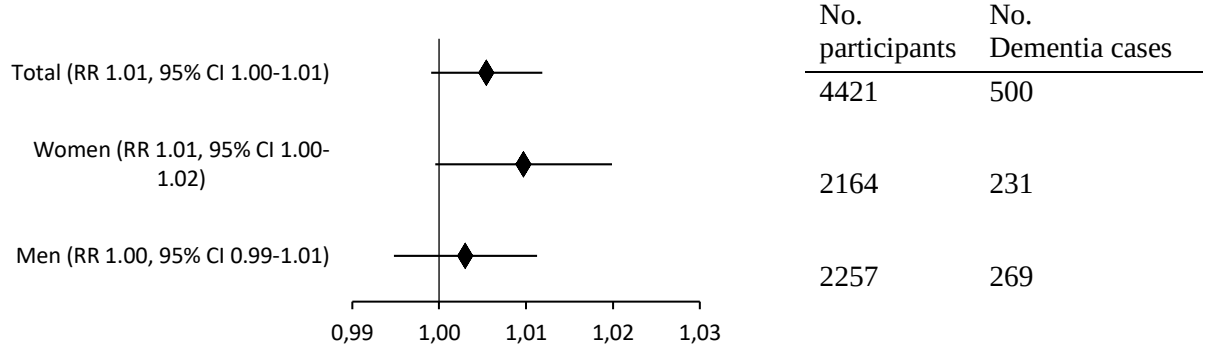
RRs for dementia for a one pack-year cumulative smoking increase is presented in Figure 2. In our analysis one pack-year increase was not significantly associated with dementia risk (RR 1.01, 95% CI 1.00-1.01, p-value 0.094, n=4421) (Figure 2). This was also the case among women and men separately (Figure 2). Results for complete cases was similar and is shown in Figure 3.

Table 4: Association between smoking status and incident dementia for the total population and stratified by gender

		No. Participants	No. Dementia cases	Crude, RR (95% CI) *P-value*	Model A, RR (95% CI) *P-value*	Model B, RR (95% CI) *P-value*	Model C, RR (95% CI) *P-value*
Total							
	Never smokers	3,823	604	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Former smokers	2,934	432	0.93 (0.82, 1.05) *0.263*	1.03 (0.91, 1.17) *0.593*	1.05 (0.92, 1.19) *0.475*	1.03 (0.90, 1.18) *0.685*
	Current smokers	1,775	269	0.96 (0.83, 1.11) *0.570*	1.35 (1.17, 1.57) *0.000*	1.31 (1.12, 1.52) *0.000*	1.36 (1.17, 1.59) *0.000*
Women							
	Never smokers	2,413	442	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Former smokers	1,312	177	0.74 (0.62, 0.88) *0.001*	0.97 (0.82, 1.16) *0.773*	0.99 (0.83, 1.18) *0.895*	0.97 (0.81, 1.17) *0.772*
	Current smokers	1,002	161	0.88 (0.73, 1.05) *0.155*	1.41 (1.17, 1.70) *0.000*	1.38 (1.14, 1.66) *0.001*	1.45 (1.19, 1.76) *0.000*
Men							
	Never smokers	1,410	162	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Former smokers	1,622	255	1.37 (1.12, 1.67) *0.002*	1.16 (0.95, 1.41) *0.147*	1.15 (0.94, 1.40) *0.186*	1.09 (0.89, 1.34) *0.417*
	Current smokers	773	108	1.22 (0.95, 1.55) *0.115*	1.34 (1.05, 1.71) *0.019*	1.26 (0.98, 1.61) *0.073*	1.26 (0.98, 1.62) *0.077*

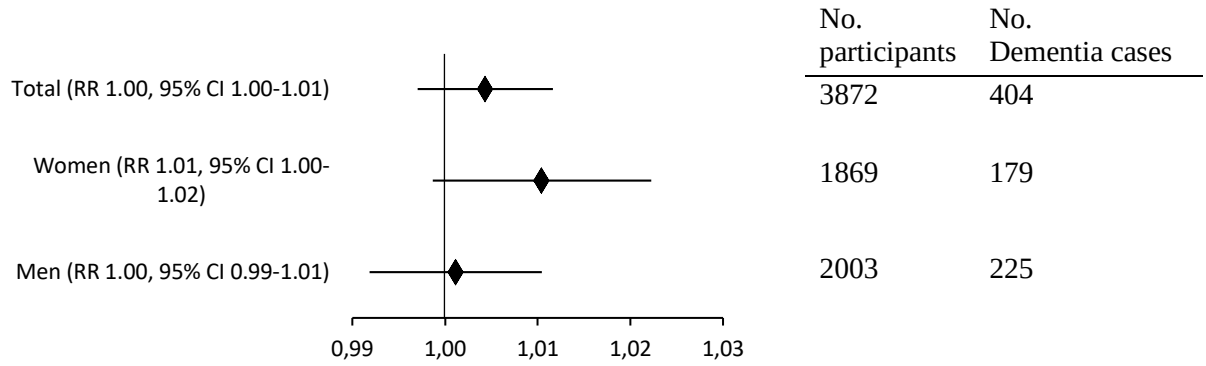
Model A was adjusted for age, Model B (main analysis) was adjusted for age + sex + other confounders (education, marital status, alcohol consumption and psychological distress), Model C was adjusted for age + sex + other confounders + covariates (BMI, diabetes, SBP, hearing loss, PA, apoplexia, sleep disturbance, IHD and cholesterol)

Figure 2: Association between cumulative smoking (pack-years) and dementia risk for the total population



The analysis was adjusted for age, sex and other confounders (education, marital status, alcohol consumption and psychological distress)

Figure 3: Association between cumulative smoking (pack-years) and dementia risk for complete cases



The analysis was adjusted for age, sex and other confounders (education, marital status, alcohol consumption and psychological distress)

5 Discussion

5.1 Key results

In this longitudinal study on a large Norwegian population-based cohort we found an association between current smoking at baseline and increased risk of developing dementia. This association was stronger among women, but no statistically significant associations were found among men. There was no association between former smoking and the risk of dementia in our analysis. When investigating the relationship between a one pack-year increase and dementia risk, we did not find statistically significant associations.

5.2 Limitations and strengths

The strengths of this study include its longitudinal, population-based cohort design, long follow-up period and large sample size. Other strengths are the high quality of standardized cognitive assessment and diagnostic procedures, and the inclusion of a comprehensive collection of relevant variables which could confound, moderate, or mediate the association between smoking and dementia.

There are potential limitations to this study which should be considered when interpreting our findings. Firstly, information on smoking exposure and the majority of covariates was self-reported and collected through questionnaires. These data may be influenced by recall bias, misreporting and differential understanding and interpretation of the questions. Participants might for instance have underreported or overreported their smoking history, which would in turn weaken or strengthen the association between smoking and dementia.

In our study we could only include participants who had survived long enough to be included in the follow-up assessment. Consequently, participants were lost and incident dementia cases might have been overlooked. There was no cognitive assessment between baseline and follow-up, meaning that participants could have developed clinical dementia and not been able to participate in or died before HUNT4 70+. This is a type of selection bias referred to as the competing risk of death or survival bias. Our study is very likely to be affected by this. Furthermore, smokers have an increased mortality compared to non-smokers due to several causes. The association between smoking and particular cancers and vascular and respiratory diseases is well established, and the list of diseases attributable to smoking continues to expand with additional studies. In high-income countries smoking of manufactured cigarettes is the biggest cause of premature death (36). Differences in death rates among smokers and non-smokers imply that smokers lose on average at least a decade of life (11). This competing risk introduces some uncertainty to the association between smoking and dementia because smokers are at higher risk of death before the age at which they might have developed dementia (12). If one assumes that smokers had higher death rates than non-smokers, the incidence of dementia in smokers might appear lower than it actually is, and the true effect of smoking exposure on dementia risk might actually be larger than indicated by the results of this study (23). The survivors in the smoking group are also likely to be healthier than those who did not survive long enough to receive a dementia diagnosis. In such a case one is comparing the incidence of dementia in non-smokers with that in the healthiest smokers (74). The baseline variables are also likely to be affected by survival bias. In our population current smokers had a lower BMI, a lower BP and less diabetes. This is the opposite of what we normally would have expected. This emphasizes the fact that we are probably comparing non-smokers with the healthiest smokers.

There are also some limitations to consider regarding the outcome variable. Firstly, some of the participants in HUNT4 70+ might have lived with dementia prior to HUNT4 70+, meaning that we do not have an exact time of diagnosis. Secondly, participants were not screened for dementia at baseline. However, one may argue that the presence of clinical dementia is highly unlikely 18-23 years prior to dementia assessment in HUNT4 70+. If some of the participants had dementia at baseline, they are very likely to have died before follow-up, and consequently they are not included in our study.

Another limitation is that smoking status was measured and fixed at baseline in HUNT2. We do not know if the participant changed their smoking habits in the years between exposure

measurement and cognitive assessment. Previous smokers might have begun smoking again, and current smokers might have quit smoking or continued smoking but with a different intensity. This change in smoking status might affect the results of this study by weakening or strengthening the association between smoking and dementia risk. If a participant who smoked daily at baseline quit smoking before the follow-up assessment, the observed association would be weakened. However, we also included cumulated packyears up to the year of follow-up in our analysis, and here the smoking amount in the 18-23 years between baseline and follow-up was accounted for. Contrarily, confounders and covariates were fixed at baseline in HUNT2 in all analyses. Any events occurring later than baseline would not have been accounted for in our analysis, e.g. if the participant developed diabetes or started excessively drinking.

Another limitation is that the term "former smoker" is non-specific and could equate persons who smoked for a short period and persons who smoked heavily for decades. This might introduce some uncertainty to the relationship between former smoking and dementia risk. Furthermore, in our study the category former smokers comprised participants who had quit smoking before participating in HUNT2. If one assumes that they did not reinitiate smoking between baseline and follow-up, they had been ex-smokers for at least 18-23 years when they were assessed in HUNT4 70+. Some studies suggest that prolonged smoking cessation is associated with a decreased dementia risk (75) and that this effect may already begin to take place three years after quitting smoking (76). Consequently, when assessing participants who have been former smokers for two decades, the risk of dementia may be reduced to the point where one does not find an association any longer.

Although we adjusted for the putatively most important potential confounders and covariates in our analyses, other unmeasured factors may have affected our results. For instance, we did not include data on cohabitation. However, in the elderly population in Norway there generally appears to be an association between marital and cohabitation status. It seems to be less common for individuals to cohabit without being married, and vice versa. We also did not assess the influence of genetic factors such as apolipoprotein E (APOE) genotype. The APOE ε4 allele is strongly associated with an increased risk of late-onset AD and is also linked to the development of VaD, Lewy body dementia and frontotemporal dementia (77, 78). Studies have shown that APOE genotype modifies the association between smoking and dementia (77). A meta-analysis found that smoking was only associated with an increased risk of AD in APOE ε4 non-carriers, possibly because the presence of one or two APOE ε4 alleles elevates

the dementia risk to such a degree that exposure to other risk factors, including smoking, increases the risk very little or not at all (27).

Lastly, complete data was not available for all subjects, but logical and multiple imputation was performed to mitigate this.

5.3 Comparisons with previous studies

Our findings are consistent with the results of several recent studies, systematic reviews, and meta-analyses (21-28). Like many studies we found a positive association between current smoking and an increased risk of dementia development while failing to find a clear association between former smoking and an increased dementia risk (25-27). We also found associations between current smoking and dementia in women, but not in men. This contrasts with some previous studies in which the authors indicated that the effect of smoking on dementia is the same for both sexes (22, 23). To our knowledge no other studies have found a significant difference in dementia risk between male and female smokers.

5.4 Interpretation

In our study we found that smoking increases the risk of dementia. This is consistent with results from several other studies, and in support of the already widely accepted theory that smoking is a risk factor for dementia. In analyses of smoking amount (pack-years) results were non-significant. However, these results reflect the results from the main analysis. They show a tendency towards increased risk with increased smoking amount for the total population and among women, but not among men (Figure 2). We found no association between former smoking and the risk of dementia, although this could be because the term is rather non-specific and that individuals in this group probably had not smoked for over two decades.

Our findings indicated that current smoking women have a higher risk of developing dementia than current smoking men. Among men we found no significant associations. However, although the found associations were not statistically significant, they still point in the direction of an increased dementia risk (Table 4). In our study there were more women than men in total, and more current smoking women than current smoking men, and this could have contributed to the observed tendencies. We also do not know the characteristics of the participants lost between baseline and follow-up, and it is possible that results have been affected by selection bias. As mentioned earlier survival bias could result in a weaker

association between smoking and dementia because smokers are at higher risk of death. Women have a higher life expectancy than men, and men are also at higher risk of cardiovascular death which is associated with smoking. As a result we could have lost more men than women between baseline and follow-up, and more of the current smoking women could have lived long enough to be included in the follow-up than current smoking men. This could have caused us to find a weakened but significant association with dementia among women, and an association with dementia weakened to the point on non-significance among men. In our study population clinical properties did not seem normally distributed compared to what we would have expected in the general population, e.g. that smokers had less diabetes than never smokers. Properties and characteristics that differ between women and men other than cardiovascular risk could have affected who survived and who did not, which again could have affected our selected population. The observed differences could possibly reflect this and not necessarily differences in dementia risk due to smoking.

In contrast to this, we found that male former smokers had higher RRs than female former smokers (Table 4). This could have been affected by the higher proportion of men in the former smoker category. Furthermore, these findings were non-significant, and risk for both former smoking women and men were close to one. Therefore, these results should probably not be emphasized too greatly.

To our knowledge no other studies on this matter have found significant differences between women and men. This could be explained by differences in study population and study design.

Important considerations for the findings in our study is that we only included data on participants that survived long enough to participate in the follow-up. This means that we could not account for survival bias and might have lost incident dementia cases between baseline and follow-up. We also did not have any genetic data on the dementia cases in the population. It is possible that some of the participants developed dementia due to hereditary predispositions.

There are several possible biological mechanisms which might explain the reported association between smoking and dementia development. As mentioned previously, explanations could be neurotoxicity due to oxidative stress, inflammation, and atherosclerosis or the link between cigarette smoking and cardiovascular impairment.

5.5 Generalizability

Our study population consists of Norwegians, which may limit the generalizability of our findings. The fact that the reference study population has fewer immigrants and a lower level of education could also impact the representativeness of the results.

6 Conclusion

The present study found an association between tobacco smoking and the incidence of dementia. Our findings stress the importance of initiatives against smoking in the general population. This study found a sex difference in risk for dementia among current smokers, but we are not able to reach any conclusion since our results are very likely to be affected by selection bias. Additional studies are needed to further investigate the differences in risk between male and female smokers, and this should be done while taking into account the competing risk of death.

7 Declaration of competing interest

The authors declare that they have no competing financial interest or personal relationships that could have influenced the work reported in this paper.

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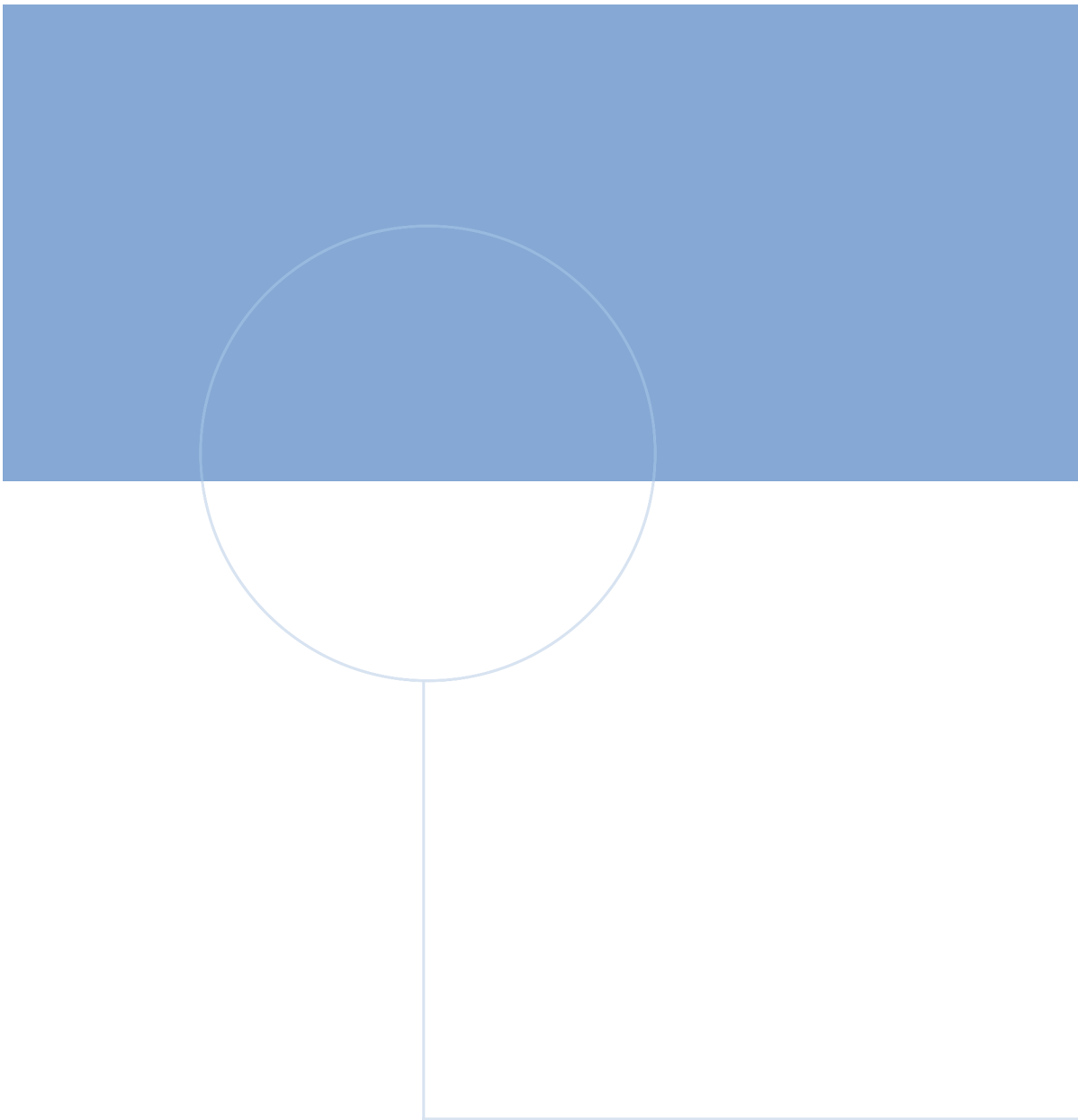

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