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Hege Rasmussen Eid

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A study based on a systematic review, narrative interviews with family caregivers and data from the HUNT Studies and a dementia register

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Frontotemporal demens: tidlige symptomer og modifiserbare risikofaktorer

Frontotemporal demens (FTD) rammer ofte yngre personer (45-65 år). Det er gjort lite forskning på modifiserbare (påvirkbare) risikofaktorer for FTD og på den tidlige sykdomsfasen av FTD. I Norge tar det gjennomsnittlig 5 år å få satt riktig diagnose hos en person med FTD. Dette medfører belastning for pårørende, kan medføre feil behandling av pasientene samt utfordringer i forhold til forskning på FTD. Formålet med avhandlingen var å få en oversikt over studiene som har undersøkt modifiserbare risikofaktorer for FTD, å studere pårørendes erfaringer fra den tidligste sykdoms fasen av FTD og å studere angst, depresjon, røyking og overvekt som risikofaktorer for FTD.

Det er brukt både kvalitativ og kvantitativ metode i avhandlingen. I Studie 1 ble det gjennomført en oversiktsartikkel over studier som har undersøkt modifiserbare risikofaktorer for FTD. I Studie 2 ble pårørende til personer med FTD intervjuet om deres opplevelser av den tidligste sykdomsfasen av FTD. Studie 3 og Studie 4 undersøkte modifiserbare risikofaktorer for FTD sammenlignet med en kontrollgruppe med pasienter med Alzheimers sykdom (AD) og en kontrollgruppe med kognitivt friske personer. Data på risikofaktorer og kontrollvariabler ble hentet fra Helseundersøkelsen i Nord-Trøndelag (HUNT), HUNT1 studien (1984-1986) og HUNT2 studien (1995-1997). FTD og AD diagnoser ble hentet fra Demensregisteret i Nord-Trøndelag og den kognitivt friske kontrollgruppen ble hentet fra et oppfølgningsprosjekt på hukommelse og intelligens etter HUNT3 studien (2006-2008).

Studie 1 viste at det er ikke gjort nok forskning på modifiserbare risikofaktorer for FTD til å kunne komme med anbefalinger om forebygging. Studie 2 viste at pårørende opplevde de første endringene ved FTD som endringer i relasjonen til den som senere fikk diagnosen FTD. Disse endringene var diffuse, vanskelig å tolke og vanskelig for pårørende å forklare, noe som kan være medvirkende faktorer til sen FTD diagnose. Studie 3 viste sammenheng mellom angst og FTD og mellom depresjon og AD. Studie 4 viste sammenheng mellom overvekt og FTD og sammenheng mellom røyking og AD og mellom overvekt og AD.

Navn kandidat: Hege Rasmussen Eid
Institutt: Institutt for psykisk helse
Veiledere: Eystein Stordal, Tor Atle Rosness, Ingela Enmarker, Ove Hellzen
Finansieringskilde: Hege Rasmussen Eid ble tildelt en forskerrekruttstilling ved NTNU. Stillingen var et samarbeidsprosjekt mellom Helse Midt-Norge og St. Olavs Hospital. Studien er finansiert av Helse Midt-Norge.

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tirsdag 05.11.19, kl. 10.00.

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Original Publications (paper 1-4)

Appendix 1- Informant letter to the participants in Study 2
Appendix 2- Interview guide used in Study 2
Appendix 3- Questionnaires in HUNT1
Appendix 4- Questionnaires in HUNT2

Preface

I have many thoughts of "why;" I think of it mostly all day long. Why did she get this disease and how am I going to handle the future? This is not how we planned our lives (crying). Things do not always turn out the way we plan it but…I struggle to find out why...to find an answer...Why did she get the disease? Except from her father, who got Alzheimer's, no other family members of hers have dementia (Husband, 52 years old).

The husband quoted above is one of the informants interviewed in one of the studies in this thesis. This quote gives insight into how a family member experiences a loved one having frontotemporal dementia (FTD). Additionally, it provides insight into the questions that family caregivers might have about FTD and may ask health professionals. Why did their loved one get this disease?

I remember thinking…already ten years ago...what is going on? He used to be a jovial and social person, but now he was so distant. We visited the GP and I tried to explain the situation. The GP suspected depression, but I knew he wasn't depressed. It was an incredibly frustrating period; they didn't listen to me (wife 60 years old).

The wife quoted above is another informant interviewed in the aforementioned study. This quote gives insight in a situation experienced by many family caregivers of persons with FTD: a delay in diagnosis. This is a common problem with serious consequences for both the patients suffering with FTD and their family caregivers. This wife experienced changes in her husband for ten years prior to receiving a diagnosis.

My interest in FTD began in 2008; at that time, I was working shifts at a nursing home in a psychogeriatric unit. A few patients residing in the facility had an FTD diagnosis. I realized that there was very little information about the disease available for both family caregivers and the nursing home staff. Additionally, I noticed that patients with FTD were extremely vulnerable; their behavioral and personality changes often woke fear and anger among the nursing home staff, and the caregiving they required was challenging.

In 2012, I began working at the Psychogeriatric Unit, Namsos Hospital. My clinical experience at this unit increased my interest of FTD, and in 2014 I began working on a project protocol for my PhD project on FTD.

During my clinical experience and while working on the literature review of the project protocol, I recognized that diagnosing FTD is a challenging task, and a delay in receiving an FTD diagnosis is common. I also realized that there was a gap of knowledge in the research field regarding modifiable risk factors for FTD.

The aim of this thesis was to contribute to research on the early stages and modifiable risk factors of FTD.

Hege Rasmussen Eid, Namsos, August 2019.

Oppsummering

Bakgrunn:

Demens er en ledende årsak til funksjonshemming blant eldre voksne over hele verden og en av de største globale utfordringene vi har (1). Verdens helseorganisasjon (WHO) har utarbeidet en global handlingsplan for 2017-2025, som blant annet skal redusere risikoen for demens og sikre en tidlig demensdiagnose (2). For å forebygge demens og bestemme kurativ behandling, er det viktig å identifisere risikofaktorer (3, 4). Modifiserbare risikofaktorer kan påvirkes av for eksempel endringer i livsstil (5). For å kunne studere og identifisere risikofakoterer for demens, så er man avhengig av at demensdiagoser stilles.

Frontotemporal demens (FTD) er en neurodegenerativ sykdom som oftest rammer personer i alderen 45 til 65 år, men kan også ramme yngre eller eldre mennesker (6). Symptomene inkluderer endringer i personlighet og atferd (7) og ofte psykiatriske symptomer som depresjon, tvangshandlinger, tvangstanker, psykose og mani (8). Disse symptomene blir ofte tolket som neurologiske eller psykiatriske sykdommer av klinikere (7). Dette bidrar til at det i dag tar gjennomsnittlig 5 år å stille en FTD diagnose (9), noe som medfører bekymring og stress for pårørende fordi de ikke kan søke hjelp og rådgivning (10).

Det finnes ikke medikamentell behandling som kan helbrede eller bremse sykdomsforløpet ved FTD i dag. Når dette forhåpentligvis kommer på plass, så blir det viktig at FTD diagnosen stilles før sykdommen har utviklet seg for langt (11). Pårørende er ofte de som ser de første endringene ved demens og kan derfor bidra med viktig informasjon under arbeidet med å stille diagnosen (12). Selv om forsinkelse i FTD diagnose er vanlig og pårørende blir regnet som viktige informanter når det gjelder de tidligste symptomene på FTD, så er det få studier som har undersøkt pårørendes erfaringer fra fordiagnostisk fase av FTD (12). Så vidt vi vet, er det bare en kvalitativ studie som har utforsket pårørendes erfaringer og behov fra tidlig sykdomsfase til institusjonalisering (13).

Det gjort svært få studier på modifiserbare risikofaktorer for FTD (14). Om lag 60% av FTD tilfeller er sporadiske, det vil si at det ikke foreligger demens i familien til den som har fått FTD (15, 16).Ved disse tilfellene kan modifiserbare risikofaktorer være en del av årsaken til sykdomsutvikling. Årsaken til mangelen på studier på modifiserbare risikofaktorer for FTD kan være mangel på diagnoseregister med store nok populasjoner med FTD kasus. I tillegg kan det være vanskelig å gjennomføre longitudinelle studier hvor det er mulig å undersøke

risikofaktorer flere år før FTD diagnosen settes. Longitudinelle studier er best egnet når det gjelder å identifisere modifiserbare risikofaktorer for demens (5).

Kunnskap om tidlige symptomer for FTD og kunnskap om modifiserbare risikofaktorer for FTD henger sammen. Det å kunne gjenkjenne og oppdage tidlige symptomer for FTD vil kunne gi mulighet for tidlig diagnosesetting og tidlig behandling og forebygging av risikofaktorer. Dersom det hadde vært mulig å igangsette livsstilsendringer tidlig i sykdomsprosessen, så ville det kanskje ha forebygget eller utsatt demenssykdommen (17). Kliniske FTD diagnoser er også nødvendige for å kunne gjennomføre epidemiologiske studier på FTD (18). Forståelsen av hvordan FTD utvikler seg fra de tidligste symptomene oppstår er også viktig i forhold til å kunne forstå om en risikofaktor er genuin eller en del av prodromalfasen av FTD.

Det overordnede målet for denne avhandlingen er å øke kunnskapen om FTD basert på kunnskapshull som medfører store konsekvenser for personer som lider av FTD og deres pårørende.

To kunnskapshull skiller seg ut når det gjelder FTD:

- Forsinkelse i FTD diagnosen.
- Mangel på kunnskap om modifiserbare risikofaktorer for FTD.

Konsekvensen av forsinkelse i FTD diagnosen kan være feildiagnostisering og feilbehandling av personer med FTD samt økt stress og belastning hos pårørende. Konsekvensen av lite kunnskap om modifiserbare risikofaktorer for FTD er mangel på muligheter for forebygging og behandling. Det overordnede målet i avhandlingen var å øke kunnskapen om de tidligste symptomene av FTD og å øke kunnskapen om modifiserbare risikofaktorer for FTD.

Basert på ovennevnte, så lurte vi på om det var mulig å undersøke pårørendes opplevelser av den tidligste sykdomsfasen av FTD ved å utføre narrative intervjuer. Kunne pårørendes erfaringer belyse noen av utfordringene ved å få stilt FTD diagnose og kunne det komme frem ny kunnskap som kan brukes for å hjelpe klinikere med å stille tidligere FTD diagnose? En kvalitativ metode og bruk av dybdeintervju ble vurdert å være mest hensiktsmessig for å besvare denne problemstillingen. Kvalitative studier undersøker og forsøker å forstå sosiale prosesser, interaksjoner og erfaringer i komplekse situasjoner (19). Dette er vanskelig å undersøke ved kvantitative metoder (20). Dybdeintervju med hver enkelt informant gir intervjuer/forsker muligheten til å gå i dybden i informantens personlige erfaringer (20).

Vi så også at det var et behov for å få en oppdatert oversikt over modifiserbare risikofaktorer for FTD, da dette ville utgjøre et fundament for videre studier på modifiserbare risikofaktorer for FTD. Vi vurderte at en systematisk oversiktsartikkel ville være best egnet til å svare på denne problemstillingen. Systematiske oversiktsartikler er blitt viktige i helsevesenet, da klinikere bruker dem for å ha oversikt over feltet. Systematiske oversiktsartikler kan også utgjøre et utgangspunkt for utvikling av kliniske retningslinjer samt utvikling av forskningsprosjekt (21). Det primære formålet for oversiktsartikler er å oppsummere hva man vet og hva man ikke vet og danner ofte grunnlag for nye studier (21).

Til slutt lurte vi på om det var mulig å studere modifiserbare risikofaktorer for FTD. Ved å bruke Demensregisteret i Nord-Trøndelag så hadde vi mulighet til å sammenligne en populasjon med FTD kasus med en kontrollgruppe med Alzheimers sykdom (AD). Vi hadde også mulighet til å bruke en kontrollgruppe med kognitive friske eldre hentet fra et oppfølgningsprosjekt på hukommelse og intelligens etter HUNT3 studien. Vi hadde muligheten til å bruke data på mulige risikofaktorer fra HUNT1 studien (1984-1986) og HUNT2 studien (1995-1997). Ville det være likheter eller ulikheter mellom FTD og AD i forhold til modifiserbare risikofaktorer? Vi bestemte oss for å gjøre to kvantitative studier på modifiserbare risikofaktorer for FTD. Kvantitativ forskningsmetoder er hovedsakelig brukt til å måle og analysere forhold mellom variabler (22).

Ettersom psykiatriske symptomer er vanlige ved FTD, så fant vi det interessant å studere angst og depresjon som risikofaktorer for FTD. Så vidt vi vet, har ingen andre studier undersøkt angst og depresjon som risikofaktorer for FTD. Ettersom røyking og overvekt er kjente risikofaktorer for AD, så fant vi det interessant å studere røyking og overvekt som risikofaktorer for FTD.

Formål

- Å få en oversikt over studiene som har undersøkt modifiserbare risikofaktorer for FTD og en oversikt over om noen modifiserbare risikofaktorer er avdekket.

- Å studere pårørendes erfaringer fra den før-diagnostiske fasen av FTD og å belyse noen av utfordringene relatert til å sette en FTD diagnose.

- Å studere angst, depresjon, røyking og overvekt som risikofaktorer for FTD sammenlignet med en kontrollgruppe med AD og en kognitivt frisk kontrollgruppe.

Forskningsspørsmål:

- Hvor mange studier har undersøkt modifiserbare risikofaktorer for FTD og hva sier funnene?

- Hva er pårørendes erfaringer fra den fordiagnostiske fasen av FTD?

- Er angst og depresjon risikofaktorer for FTD sammenlignet med AD og kognitivt friske personer? Er det forskjeller eller likheter mellom FTD og AD?

- Er røyking og overvekt risikofaktorer for FTD sammenlignet med AD og kognitivt friske personer? Er det forskjeller eller likheter mellom FTD og AD?

Metoder:

Problemstillingen og forskningsspørsmålene var av både kvalitativ og kvantitativ art og begge disse metodene er anvendt i avhandlingen.

Studier:

- Studie 1: "Risk factors for Frontotemporal dementia" er en systematisk review, en oversiktsartikkel.

- Studie 2: "Family caregivers experiences of pre-diagnostic stage of frontotemporal dementia" er en kvalitativ studie med fenomenologisk-hermeneutisk tilnærming. I

denne studien er pårørende til personer med FTD blitt intervjuet om deres erfaringer fra før-diagnostisk fase av FTD.

- Studie 3: "Anxiety and depression as risk factors in frontotemporal dementia and Alzheimer's disease: The HUNT study". Dette er en kvantitativ nøstet kasus-kontroll studie med longitudinelt design. Data på demensdiagnoser er hentet fra Demensregisteret i Nord-Trøndelag og data på risikofaktorer og kontrollvariabler er hentet fra HUNT2.

- Studie 4: "Smoking and obesity as risk factors in frontotemporal dementia and Alzheimer's disease. The HUNT Study». Dette er en kvantitativ nøstet kasus-kontroll studie med longitudinelt design. Data på demensdiagnoser er hentet fra Demensregisteret i Nord-Trøndelag og data på risikofaktorer og kontrollvariabler er hentet fra HUNT1.

Resultater:

- Studie 1: "Risk factors for Frontotemporal dementia". Tolv artikler som omhandlet modifiserbare risikofaktorer for FTD ble inkludert i oversiktsartikkelen. Av disse fant en studie diabetes som risikofaktor for FTD, tre studier fant hodetraume som risikofaktor for FTD og en studie fant autoimmun sykdom som risikofaktor for primær progressiv afasi (en undergruppe av FTD).

- Studie 2: "Family caregivers experiences of pre-diagnostic stage of frontotemporal dementia" Studien viste at pårørende opplevde de første endringene ved FTD som endringer i relasjonen til den som senere fikk diagnosen FTD. Disse endringene var diffuse, vanskelig å tolke og vanskelig for pårørende å forklare for andre.

- Studie 3: “Anxiety and depression as risk factors in frontotemporal dementia and Alzheimer’s disease: The HUNT study”. Studien viste signifikant sammenheng mellom angst og FTD og mellom depresjon og AD.

- Studie 4: “Smoking and obesity as risk factors in frontotemporal dementia and Alzheimer’s disease. The HUNT Study”. Studien viste signifikant sammenheng mellom overvekt og FTD og signifikant sammenheng mellom røyking/overvekt og AD.

Konklusjoner:

- Studie 1: “Risk factors for Frontotemporal dementia”. Det er ikke gjort nok forskning på modifiserbare risikofaktorer for FTD til å kunne komme med anbefalinger om livsstilsendringer for å forebygge FTD.

- Studie 2: “Family caregivers experiences of pre-diagnostic stage of frontotemporal dementia” Pårørende opplevde den før-diagnostiske fasen av FTD som svært belastende og vanskelig. Dette, i tillegg til at det var vanskelig å fortelle om og beskrive symptomene for andre og at de ikke alltid ble tatt på alvor av klinikere, kan bidra til at FTD diagnosen blir satt for sent.

- Studie 3: “Anxiety and depression as risk factors in frontotemporal dementia and Alzheimer’s disease: The HUNT study”. Angst er risikofaktor for FTD mens depresjon er risikofaktor for AD.

- Studie 4: “Smoking and obesity as risk factors in frontotemporal dementia and Alzheimer’s disease. The HUNT Study». Overvekt er risikofaktor for FTD, mens både røyking og overvekt er risikofaktorer for AD.

Denne avhandlingen har bidratt til økt kunnskap om tidlige symptomer på FTD opplevd av nærmeste pårørende, om forskningsfeltet på modifiserbare risikofaktorer for FTD og om angst, depresjon, røyking og overvekt som risikofaktorer for FTD sammenlignet med AD.

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The present thesis was written as part of the doctoral program at the Department of Mental Health, Faculty of Medicine and Health Sciences, The Norwegian University of Science and Technology (NTNU), Trondheim. The Central Norway Regional Health Authority funded this PhD project.

Two of the studies in this dissertation use data from the Dementia Register of Nord-Trøndelag, established in 2005 by Eystein Stordal.

Two of the studies in the thesis use data from the Nord-Trøndelag Health Study (the HUNT study). The HUNT study is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU)), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Two of the studies in this thesis use a control group selected from a follow-up project performed by Ole Bosnes et al. on memory and intelligence after HUNT3.

Several people have made this thesis possible to carry out and, therefore, I would like to express gratitude to the following:

The informants for participating in the interviews for my qualitative study. Your participation has contributed to important knowledge on early stage frontotemporal dementia.

Sigrid Sando, MD, Ph.D. for great assistance in finding participants for my qualitative study.

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Special thanks to my family and friends for supporting me.

To my husband Tom Arve and our children Nora Kristin and Iver Mathias:

Thank you for being proud of me and for your love.

List of papers

This dissertation includes four papers. The papers will be referred to by numbers as indicated below:

1: Rasmussen H, Stordal E, Rosness T.A.

Risk factors for frontotemporal dementia.

Tidsskriftet Den Norske Legeforening. 2018 Sep; 138(14): 1343-7.

2: Rasmussen H, Hellzen O, Stordal E, Enmarker I.

Family caregivers experiences of pre-diagnostic stage of frontotemporal dementia.

Geriatric Nursing. Publication date online: 2018 Nov. In press: 2019 May-June; 40: 246-251.

3: Rasmussen H, Rosness T.A, Bosnes O, Salvesen Ø, Knutli M, Stordal E.

Anxiety and depression as risk factors in frontotemporal dementia and Alzheimer's disease: The HUNT study.

Dementia and Geriatric Cognitive Disorders Extra. 2018 Nov; 8: 414-25.

4: Rasmussen H**,** Rosness T.A, Bosnes O, Salvesen Ø, Knutli M, Stordal E.

Smoking and obesity as risk factors in frontotemporal dementia and Alzheimer's disease: The HUNT Study.

Dementia and Geriatric Cognitive Disorders Extra. 2019 Jan; 9: 1-10.

List of Abbreviations

AD: Alzheimer's disease

APOE: Apolipoprotein E

BMI: Body Mass Index (A person's body weight in kilograms divided by his or her height in meters squared).

CBD: Corticobasal degeneration

CH: In this thesis: Cognitively healthy control group

CI: Confidence Interval

CNS: Central nervous system

FTD: Frontotemporal dementia

GAD: Generalized anxiety disorder

HADS: Hospital Anxiety and Depression Rating Scale

HADS-A: Anxiety sub-scale of HADS

HADS-D: Depression sub-scale of HADS

HUNT: The Nord-Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag)

HUNT1: The Nord-Trøndelag Health Study 1984-86

HUNT2: The Nord-Trøndelag Health Study 1995-97

HUNT3: The Nord-Trøndelag Health Study 2010-11

HUNT4: The Nord-Trøndelag Health Study 2017-19

ICD-10: International Statistical Classification of Diseases and Related Health Problems

LR: Likelihood ratio

LR-: Likelihood ratio negative, likelihood for negative results

LR+: Likelihood ratio positive, likelihood ratio for positive results

MCI: Mild cognitive impairment

MeSH: Medical Subject Headings

mm Hg: millimeter of mercury

MRI: Magnetic resonance imaging

NMDA receptors: N-methyl-D-aspartate receptor; a glutamate receptor and ion channel protein found in nerve cells

OCD: Obsessive-compulsive disorder

OR: Odds Ratio

***p*-value:** probability value

PGRN: Progranulin gene

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTSD: Post-traumatic stress disorder

PSP: Progressive supranuclear palsy

REK: Regional Ethical Committee

Se-Fe: Serum ferritin

SPSS 25: Statistical Package for Social Sciences version 25.0

SSRI: Selective serotonin reuptake inhibitors

Sv-PPA: primary progressive aphasia

TAU: Tau proteins

TIA: Transient ischemic attack

TDP-43: Transactive response DNA binding protein

95% CI: 95% Confidence Interval

WHO: World Health Organization

WMA: The World Medical Association

Table of figures

Limitations in the thesis

There are limitations of note in my thesis regarding the term frontotemporal dementia (FTD).

The term FTD encompasses both FTD spectrum disorders and FTD-related disorders (23). I have briefly discussed the behavioral and language variants of frontotemporal dementia. However, I do not discuss FTD-related disorders, such as progressive supranuclear palsy, corticobasal degeneration, and behavioral variant of FTD with motor-neuron disease.

Diagnostic work, diagnostic criteria, and neuropathology for FTD and Alzheimer's disease (AD) are only briefly mentioned in the thesis.

The main focus of this thesis is FTD; AD is, therefore, not described in as much detail as FTD in the thesis. As this thesis focuses on modifiable risk factors for FTD and AD, genetic risk factors is only briefly mentioned.

Summary

Background:

Dementia is a major cause of disability among older adults worldwide, and one of the biggest global challenges (1). World Health Organization (WHO) has developed a global action plan for 2017-2025 that aims to reduce risk of dementia and secure earlier dementia diagnoses (2). The identification of risk factors is an important key to prevent dementia and determine curative treatment (3, 4). Modifiable risk factors can be influenced by variables such as changes in life style (5). In order to study and identify risk factors for dementia, dementia diagnoses are needed.

Frontotemporal dementia (FTD) is a neurodegenerative disease most often diagnosed between ages of 45 and 65, though it may affect younger and older people as well (6). Symptoms of FTD include changes in personality and behavior (7), and are often accompanied by psychiatric symptoms such as depression, compulsions, psychosis, obsessions, and mania (8). These symptoms are often interpreted by clinicians as neurological or psychiatric disorders (7). This contributes to the fact that reaching an FTD diagnosis may take up to 5 years (9). The delay in diagnosis leaves family caregivers in a state of great concern and stress (10). Misdiagnosis or delay in correct diagnosis reduces the family caregiver's ability to seek supportive resources and management (10).

No pharmacological treatment currently exists for FTD, but as newer therapies become available in the future, it will be even more crucial to identify FTD as early as possible. Early intervention prior to disease progression in the brain is important (11). Family caregivers are often the first to notice early signs of dementia and are, therefore, important informants in the diagnostic settings (12). Despite the fact that delay of FTD diagnosis is common, and that family caregivers are important contributors of information about the earliest symptoms, few studies have investigated family caregivers' experiences with pre-diagnostic stage of FTD (12). To our knowledge, only one qualitative study has explored the experiences and needs of family caregivers of persons with FTD from the earliest stage to institutionalization (13).

There is sparse knowledge available presently regarding modifiable risk factors of FTD (14). About 60% of FTD cases are sporadic, defined as the absence of dementia diagnoses in the family of the person with FTD (15, 16). In these cases, modifiable risk factors may be significant contributors to the development of the disease. The lack of studies on modifiable

risk factors for FTD may be related to a shortage of diagnostic registers for FTD populations large enough to perform research studies. In addition, it is challenging to achieve a longitudinal design, allowing researchers to investigate risk factors several years before the dementia diagnosis is established. The identification of modifiable risk factors for dementia is best addressed through longitudinal study designs (5).

Knowledge about early symptoms and modifiable risk factors for FTD is related. Recognizing early symptoms of FTD gives the opportunity for earlier FTD diagnoses, early treatment, and prevention of risks. Preventative actions early in the disease process may prevent or delay the disease (17). Clinical diagnoses of FTD are necessary in order to perform epidemiological studies (18). Additionally, knowledge on how FTD develops from the earliest symptoms is important to understand if a risk factor is a genuine risk or a part of the prodromal phase of FTD.

The overall aim of this thesis is to increase the knowledge of FTD as a gap in knowledge in the research field leads to significant consequences for both persons suffering from FTD and their family caregivers.

Two main knowledge gaps in FTD research stand out:

- Delay in the diagnosis of FTD.
- The lack of knowledge regarding modifiable risk factors for FTD.

The consequences of a delay in diagnosis include misdiagnosis and inaccurate treatment of patients with FTD, as well as increased stress and burden to family caregivers. Regarding modifiable risk factors for FTD, this lack of knowledge results in a dearth of options for prevention and treatment. The overall aim of this thesis was to increase knowledge about the earliest symptoms and modifiable risk factors for FTD.

Based on this knowledge, we conjectured whether it was possible to gain insight by studying family caregivers' experiences regarding the earliest symptoms of FTD by performing narrative interviews. Could the experiences of the family caregivers enlighten us as to the challenges in achieving an early FTD diagnosis? A qualitative study with narrative interviews of family caregivers was considered appropriate to answer this research question. Qualitative research methods aim to investigate social processes and interactions, and to understand experiences in complex situations (19). These situations are difficult to investigate using

quantitative research methods (20). Narrative interviews give the researcher the ability to explore the personal experiences of the informants (20).

We also saw the need to get an updated overview of modifiable risk factors for FTD, as this would constitute the basis for our studies on risk factors for FTD. We decided to perform a systematic review to achieve this update. Systematic reviews have become increasingly important in health care, as clinicians read them to maintain awareness of updates in their field. Reviews are also often used as a starting point to develop clinical practice guidelines and as justification for further research (24). The primary purpose of literature reviews is to sum up what is known and what is unknown, and to lay the foundation for new studies (21).

Finally, we wondered if it was possible to study modifiable risk factors for FTD. Using the Dementia Register in Nord-Trøndelag Hospital Trust, we had the opportunity to compare a population of FTD cases with a group of Alzheimer's disease (AD) cases. We also had the opportunity to use a control group of cognitively healthy individuals selected from a follow-up project on memory and intelligence after the HUNT3 Study. We had the opportunity to use data on potential risk factors from the HUNT1 Study (1984-1986) and the HUNT2 Study (1995-1997). Would there be similarities in the risk factors for FTD and AD? We decided to perform two quantitative studies on risk factors of FTD. Quantitative research methods are primarily to measure and analyze the relationships between variables (22).

As FTD often presents with psychiatric symptoms, we included anxiety and depression when studying potential risk factors for FTD. To our knowledge, no other studies have considered anxiety and depression as potential risk factors for FTD. As smoking and obesity are known risk factors for AD and other types of dementia, we included these potential risk factors in our study, as well.

Aims:

- To obtain an overview of the number of studies that had assessed modifiable risk factors for FTD, and determine if any modifiable risk factors had been identified.

- To study the family caregiver's experiences regarding the pre-diagnostic stage of FTD, and to illuminate some of the challenges related to establishing an FTD diagnosis.

- To study anxiety, depression, smoking, and obesity as risk factors for FTD in comparison with risk factors for AD and cognitively healthy individuals.

Research questions:

- How many studies have investigated the modifiable risk factors for FTD, and what are the findings?

- What is the family caregiver's experience regarding the pre-diagnostic stage of FTD?

- Are anxiety and depression risk factors for FTD when compared with AD and cognitively healthy individuals? Are there differences or similarities in anxiety and depression as risk factors for FTD and AD?

- Are smoking and obesity risk factors for FTD when compared with persons with AD and cognitively healthy individuals? Are there differences or similarities in smoking and obesity as risk factors for FTD and AD?

Methods: Three different methods and designs have been used to answer the research questions. Textbox 1 gives an overview of the four studies in the thesis, titles of the papers, methods, and study designs.

Textbox 1: Studies, titles of papers, methods, and designs

STUDY	**I**	**2**	**3**	**4**
TITLE OF PAPER	Risk factors for frontotemporal dementia	Family caregivers' experiences of pre-diagnostic stage of frontotemporal dementia.	Anxiety and depression as risk factors in frontotemporal dementia and Alzheimer's disease: The HUNT study.	Smoking and obesity as risk factors in frontotemporal dementia and Alzheimer's disease. The HUNT Study.
METHOD	Review	Qualitative method	Quantitative method	Quantitative method
DESIGN	Systematic review	Phenomenological-Hermeneutic study	Longitudinal, nested case-control study	Longitudinal, nested case-control study

Results and conclusions: Textbox 2 contains an overview of the four studies in the thesis, titles of the papers, methods, designs, a summary of results, and conclusions from each study.

Textbox 2: Results and conclusions

STUDY	1	2	3	4
TITLE OF PAPER	Risk factors for frontotemporal dementia	Family caregivers' experiences of pre-diagnostic stage of frontotemporal dementia.	Anxiety and depression as risk factors in frontotemporal dementia and Alzheimer's disease: The HUNT study.	Smoking and obesity as risk factors in frontotemporal dementia and Alzheimer's disease. The HUNT Study.
RESULTS	One study found diabetes as a risk factor for FTD. Three studies found head injury to be risk factor for FTD One study found an association between autoimmune disease and primary progressive aphasia.	The pre-diagnostic stage of FTD was experienced as a process of changes in the interpersonal relationship with their loved one. The changes were subtle and difficult to interpret and describe to others.	Significant associations were found between anxiety and FTD. Significant associations were found and between depression and AD.	Significant associations were found between obesity and FTD. Significant associations were found between smoking and AD. Significant associations were found between obesity and AD.
CONCLUSIONS	The current evidence base of modifiable risk factors of FTD is too narrow to be able to draw any conclusions. There is not enough evidence to support recommendations for lifestyle changes to prevent FTD at a population level.	The devastating and exhausting character of the process of changes in the relationship, the difficulties of describing the subtle symptoms, and a lack of awareness in clinicians may contribute to delay in FTD diagnosis.	Anxiety is a risk factor for FTD. Depression is a risk factor for AD.	Obesity is a risk factor for FTD. Smoking and obesity are risk factors for AD

This thesis has contributed to new knowledge of the pre-diagnostic stage of FTD as experienced by family caregivers; it has brought new knowledge to the research field of modifiable risk factors for FTD, as well as the identification of anxiety, depression, smoking, and obesity as risk factors for FTD.

1 Background

1.1 Dementia

Dementia is a clinical syndrome caused by degeneration of the neurons; it is characterized by deterioration in cognitive abilities and independent living (25). The prevalence of dementia is estimated to be over 45 million people worldwide, and this number is predicted to triple by 2050 (26). Dementia is the main cause of dependency in older people, and family caregivers are primarily responsible for their future care (27). The World Health Organization (WHO) estimates over 9.9 million new cases of dementia are diagnosed each year worldwide; this is a new case every 3.2 seconds (1). The most common types of dementia are Alzheimer's Disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (FTD) (28). The most common cause for dementia in individuals over 65 years is AD. In those under 65 years, AD and FTD are the most common causes for dementia (29-31). In Norway, 1.5 percent of the entire population, approximately 80, 000 people, have dementia (25).

1.2 Alzheimer's disease

The first recognized neuropsychological description of AD was recorded by Aloysius "Alois" Alzheimer in 1907. Auguste Deter, a 51-year-old patient, presented with symptoms of marked memory impairment, language deficits, and writing difficulties. After Auguste Deters' death, Alois Alzheimer examined her brain microscopically and observed neurotic plaques, neurofibrillary tangles, and amyloid angiopathy. These became the hallmarks of the disease which would bear his name (32). AD is a progressive neurodegenerative disease that accounts for 60-80% of all dementia cases (26, 33). AD is characterized by amyloid plaques, tangles, and neurodegeneration in areas of the brain associated with cognition, such as hippocampus and the cortex (34).

Typically, early symptoms of AD include difficulties remembering recent conversations, names, or events. Late symptoms include difficulties in communication, confusion, disorientation, poor judgement, changes in behavior, and difficulty speaking, swallowing, and walking (28). The preclinical or prodromal phase can last for several decades (26). People with AD aged 65 or older survive for an average of 4 to 8 years after the diagnosis, but some live as long as 20 years post diagnosis (28).

Alzheimer's disease also include cases where symptoms have not appeared despite initial pathologic changes in the brain, and as well as patients with mild cognitive impairment (28).

1.2.1 Risk factors

In the Alzheimer's Association Report 2017, the Alzheimer's Association states that there is sufficiently strong evidence that management of cardiovascular risk factors (particularly obesity, diabetes, smoking, and hypertension), regular physical activity, and lifelong cognitive training may reduce the risk of all causes of dementia (28). The report also states that people with fewer years of education are at higher risk for AD. Fewer years of education may result in less cognitive reserve, lower socioeconomic status, and increased risk of cardiovascular risk factors (28). Some studies show that social and cognitive engagement may reduce the risk of AD, but the mechanism is unknown (28). According to the Alzheimer's Association Report 2017, traumatic brain injury (TBI) is also a risk factor for AD and other dementias (28).

The research on AD prevention has advanced in the last two decades. Despite advances in the field, research on AD poses some overall challenges. One challenge is the validity of AD diagnoses. Overlap of symptoms with other dementias, particularly early in the disease process, results in difficulty differentiating AD from other dementias (35). Additionally, AD often exists with comorbidities, such as vascular disease or Lewy body dementia (35). AD also shares risk factors with other diseases; AD and cerebrovascular disease share risk factors such as diabetes mellitus, hypertension, and dyslipidemia (36). Additionally, the direction of causality may be unclear, particularly when risk factors occur near the onset of dementia (17).

Epidemiological studies and randomized clinical trials have been used to assess both modifiable and non-modifiable risk factors for AD, but have significant limitations. Due to multiple interacting and confounding factors, it is difficult to determine causality. It is also difficult to compare studies assessing risk factors for AD due to use of different inclusion criteria (37). There is a lack of research on AD in low and middle income countries associated with lack of diagnostic tools, specialized doctors, and researchers, resulting in a lack of opportunities to participate in clinical trials (38).

The non-modifiable risk factors consider the most important for AD are advanced age (26, 28, 39), family history of dementia (28, 39), and the presence of the Apolipoprotein E allele (APOE) (28). Recent studies have identified new genetic risk factors for AD (40). Experts

believe that AD develops as a result of multiple factors, both modifiable and non-modifiable (28). As there are many studies assessing modifiable risk factors, reviews on modifiable risk factors for AD have been chosen for this section in the thesis.

The Lancet Commission on Dementia Prevention, Intervention, and Care published an extensive report on dementia prevention, intervention, and care in 2017 (17). The authors performed a meta–analysis of suitable papers discussing education, hearing, exercise and physical activity, diabetes, hypertension, obesity, smoking, depression, and social contact as modifiable risk factors for dementia. The results of this report suggested that a combination of nine risk factors contribute to 35% of dementia. These risk factors were midlife hypertension, education to a maximum of age 11-12 years, midlife obesity, late life depression, hearing loss, smoking, social isolation, and physical inactivity (17). The primary limitation of this report was a focus on evidence from high-income countries (17).

Patterson et al (2007) published a systematic review focused on longitudinal cohort studies on modifiable risk factors of dementia, AD, and vascular dementia (5). The quality of the articles included in the systematic review were considered independently by different readers. A total of 60 articles were included in the review. The review concluded that both higher and lower diastolic blood pressure was associated with increased risk of AD and vascular dementia, diabetes mellitus was associated with an increased risk for all types of dementia and AD, stroke was associated with increased risk for both all types of dementia and AD, and elevated serum cholesterol was associated with increased risk for all types of dementia and AD (5).

Povova et al (2012) performed a review on risk factors for AD, including both original and review articles. The review included 104 articles (41). Smoking was associated with significant risk of AD, especially in apoE4 allele carriers. The risk of developing dementia or AD was reduced in light to moderate alcohol consumers, but middle aged heavy drinkers had a threefold higher risk for dementia and AD later in life (especially in apoE4 allele carriers). Obesity during middle age was found to be a risk factor for AD, while a decrease in BMI in the elderly was also associated with higher risk for AD. The findings of associations between blood pressure and the risk of AD were not consistent, as short follow-up studies found no or an inverse association between blood pressure values and AD, while longer follow-up studies suggested associations between low blood pressure in later life and AD. Hypercholesterolemia and Diabetes mellitus in middle age was found to be a risk factor for AD. Both cardiovascular and cerebrovascular disease were associated with increased risk of

AD. Lower socioeconomic status, less education, poor social network, and poor social engagement were associated with an increased risk of AD. Regular physical activity and variable mental activity was considered protective against AD (41). This study reviewed a large number of articles and included studies on AD specifically, rather than dementia in general. Weaknesses of this study were a lack of critical evaluation of the quality of the studies included in the review, and a lack of description of inclusion and exclusion criteria for the articles in the review.

The Kungsholmen project in 2007 was a population-based study that addressed risk factors for AD and dementia from a lifetime perspective (42). This project found that modifiable risk factors for AD and dementia were lower education in childhood, low socio-economic status in childhood, both high blood pressure and low pressure in geriatric patients (after 75 years), heart failure in geriatric patients, diabetes mellitus in geriatric patients, and a poor social network in geriatric patients. Additionally, an increased risk of AD and dementia in men was seen with long term exposure to a higher level of extremely-low-frequency magnetic fields in adult life (42). Anemia was also found to be a potential risk factor for dementia in elderly patients. The project found that smoking does not have a protective effect against AD and dementia. Light to moderate alcohol consumption was found to be protective against AD and dementia in elderly patients (42). In the review of the Kungsholmen project, the authors conclude that two preventive strategies for dementia were good control of blood pressure both in adult life and advanced age, and an active and socially integrated life for the elderly. A significant strength of this study is the level of follow-up and the lifetime perspective (42).

1.2.2 Medical treatment

Currently, there are two classes of drugs available for medical treatment of AD: Cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and NMDA antagonists (memantine) (38). Neither class of drugs slows or halts damage of the neurons in the brain, but may temporarily improve symptoms (28).

1.2.3 Epidemiology

In 2006, the worldwide prevalence of AD was estimated to be 26.6 million, and this was expected to quadruple by 2050 (4). In 2011, approximately 33.9 million individuals lived with AD worldwide; this was anticipated a triple over the next 40 years, due to longer life expectancies (43). In 2017 in the US population, (age 65 or older), the incidence of AD was 2

new cases per 1000 people age 65 to 74, 12 new cases per 100 people age 75 to 84 and 37 new cases per 1000 people age 85 and older in 2017 (28).

1.2.4 Diagnostic criteria

Diagnosing AD requires a careful medical evaluation, often performed by neurologists or geriatricians. In addition to cognitive tests and neurologic examinations, it is necessary to obtain a medical and family history from the patient. This includes psychiatric history and history of cognitive and behavioral changes (28). Magnetic resonance imaging (MRI) of the brain may show changes in the brain, and biomarkers may be measured in the cerebrospinal fluid (28). The guidelines for diagnosing AD have been revised in 2011 by the National Institute of Aging (28).

1.3 Frontotemporal dementia

FTD was first described by Arnold Pick as Pick's disease in 1892 (23, 44). He described patients with progressive language deficits associated with atrophy in the left temporal lobe. In 1911, Alois Alzheimer performed histologic analysis of Pick`s clinical cases and found inclusions in the neurons, known as Pick's bodies (23).

The term Pick's disease was used during the 1990s, referring purely to what we know as a behavioral variant of FTD today (23). In the 1990s, the sub-types of FTD were still unknown; there was no knowledge of prevalence, limited knowledge of prognosis, and a lack of diagnostic criteria (23).

The term frontotemporal dementia encompasses several neurodegenerative diseases that lead to loss of neurons in the frontal and/or temporal lobes of the brain (45). The frontal and temporal lobes of the brain have important functions when it comes to behavior, problem-solving, planning, emotional control, and speech (6).

The symptoms of FTD include changes in personality and behavior, as well as language deficits in some cases (7). The symptoms often mimic or are often accompanied by psychiatric symptoms, such as depression, mania, compulsions, psychosis, and obsessions (8).

1.3.1 Risk factors

In some families, FTD has been linked to chromosome 17 with an autosomal dominant inheritance pattern. In other families, FTD has been linked to chromosomes 3 and 9. In certain cases, mutations in the TAU gene have been detected (46).

The findings in Study 1 show that very few studies have investigated modifiable risk factors for FTD. The studies on modifiable risk factors included for Study 1 all use validated diagnoses of FTD. However, the clinical syndrome of FTD is caused by different neuropathological diseases which may have different risk factors. Some studies used different sub-types of FTD as both cases and controls, others used FTD as cases and other dementia diseases as controls, and some used cognitively healthy controls. There is also variability in study designs. This inconsistency contributes to a weak basis of determination of causal inference for the risk factors investigated.

Most of the studies also have small sample sizes. Limitations of small sample size studies include a large standard error, wide 95% CI, and imprecise estimates of the effect. Additionally, overestimation of the magnitude of an association or false-negative results may occur (47).

The studies lack a longitudinal design, which makes it difficult to separate risk factors from prodromal phases of FTD. Although there is some uncertainty regarding the length of prodromal phase in FTD (48), it generally takes 5-10 years to make and accurate FTD diagnosis (9, 49), indicating that the prodromal phase lasts at least 5-10 years. Most of the studies are case-control studies collecting data a few years before or at the same time as the patient was initially diagnosed. This may affect responses to questionnaires and biological variables studied in the cases and controls, a disadvantage of case-control studies (50).

The symptoms of FTD include behavioral changes such as changes in eating habits with preferences of sweets and carbohydrates, and increased use of tobacco and alcohol (8, 45, 51). In case-control studies, a retrospective design goes from disease development backwards in time. The disease may affect the validity of recalled historical information, and may result in reversed causation (50). Separating symptoms of the prodromal phase of FTD and risk factors of FTD (such as obesity, diabetes, smoking, use of alcohol) in longitudinal studies is necessary. Similarly, when assessing head trauma as risk factor for FTD, we must consider that the symptoms of FTD may include impulsive or careless actions and criminal behaviors (45).

Discussion of the studies included in Study 1

A study by Golimstok et al (2014) aimed to assess cardiovascular risk factors in frontotemporal dementia (52).
Design: Prospective case-control study conducted over a period of four years (2003-2007).
Cases and controls: 100 cases of FTD and 200 controls of cognitive healthy individuals.
Data on dementia diagnosis: The FTD cases met the Lund and Manchester criteria for FTD diagnosis.
Risk factors: Gender, age, diabetes mellitus, hypertension, obesity, dyslipidemia, hypothyroidism, and osteoporosis.
Data on risk factors: Obtained from the medical records of the cases and controls during a four-year period (2003-2007). The diagnosis of diabetes was based on medical history, current treatment, and results of direct measurements. Diabetes was diagnosed based on fasting plasma glucose level >7.0 mmol/l or 126 mg/dl.
Findings: Diabetes was found as an independent risk factor for FTD.
Strengths of the study: Validated FTD diagnosis and data on risk factors of good quality.
Weakness of the study: Small population of individuals with FTD. Lack of longitudinal design. As the diagnosis of FTD was already set, it is likely to believe that many of the cases had developed cognitive decline. Persons with a cognitive decline may forget to fast before blood tests are performed, resulting in invalid measurements of fasting plasma glucose levels. Also, the finding of diabetes as a risk factor of FTD may actually be related to behavioral changes in the prodromal phase of FTD.

A study by Atkins et al (2012) aimed to assess cerebrovascular risk factors in early-onset dementia (53).
Design: Case-control study.
Cases and controls: 62 cases with early onset AD and 61 controls of early onset FTD.
Data on dementia diagnosis: Both FTD cases and AD controls were diagnosed using published criteria and MRI, SPECT, PET, and genetic analysis.
Risk factors: Hypertension, high cholesterol, diabetes, smoking, BMI, cardiovascular disease, vascular disease, and use of statins and hormone–replacement therapy were assessed as modifiable risk factors for FTD.
Data on risk factors: Data on smoking was self-reported and grouped into “never,” “ex,” and

"current." The spouse/caregiver confirmed the data and information collected from primary physicians. Weight and height were measured by a neurologist, and BMI was calculated and grouped into underweight (BMI>18.5), normal (18.5 – 24.9), overweight (25 – 29.9), and obese (30+).
Findings: Significant associations was found between smoking, elevated BMI, and FTD.
Strengths of the study: Validated dementia diagnoses.
Weakness of the study: The findings in this study may be a reflection of the prodromal phase of FTD, due to the lack of longitudinal design. The study also had a small population and assessed many risk factor variables. The data on smoking was self-reported and confirmed by spouse/caregiver. The self-reported data on smoking may be influenced by cognitive decline in the respondents, and it may be difficult for the spouse/caregiver to disagree with the respondent.

Kalkonde et al (2012) aimed to assess medical and environmental risk factors for frontotemporal dementia in a veteran population (54).
Design: Case-control study.
Cases and controls: This case-control study compared 63 cases of a behavioral variant of FTD with 491 controls with another type of dementia (Alzheimer's disease, vascular dementia, dementia with Lewy bodies).
Data on dementia diagnoses: Cases and controls were recruited between 2003 and 2008 at a medical center; patients were evaluated by neurologists, and dementia diagnoses were obtained using standardized criteria. FTD was diagnosed by using the Neary criteria.
Risk factors: Data were collected on age, gender, neurological diagnoses, hypertension, diabetes, hyperlipidemia, cardiac disease, cerebrovascular disease, current tobacco and alcohol use, diagnoses of cancer, anemia, chronic obstructive pulmonary diseases, renal failure, heart failure, thyroid disease, atrial fibrillation, and traumatic brain injury. The presence of the risk factor had to precede the onset of dementia to be considered valid.
Data on risk factors: The data of risk factors were collected by medical school graduates blinded to the study design. The data on traumatic brain injury was self-reported and, in some cases, confirmed by family caregiver/loved one.
Findings: Lower prevalence of heart disease and cerebrovascular disease were found in the FTD group than the control group of other types of dementia.
Strengths of the study: Validated dementia diagnoses.
Weakness of the study: This study lacks a longitudinal design, had a small number of cases,

and assessed many risk factors. Additionally, there is the possibility of recall bias in the self–reported data, and no information on the severity and timing of the head injury.

De Reuck et al (2012) aimed to assess cerebrovascular lesions in patients with frontotemporal lobar degeneration (55).
Design: Case-control neuropathological study.
Cases and controls: The study compared 22 brains from deceased persons diagnosed with FTD to 15 brains from deceased persons with no history of disease.
Data on dementia diagnosis: The neuropathological diagnosis of FTD was made post-mortem by neuropathological evaluation blinded to history and clinical data.
Risk factors: Cerebrovascular lesions (hemorrhage, infarcts, and lacunae), vascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking), and antithrombotic treatment.
Data on risk factors: Cerebrovascular lesions (hemorrhage, infarcts, and lacunae) were detected on microscopic examination. Vascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking) and antithrombotic treatment were also assessed.
Findings: The vascular risk factors and use of antithrombotic treatment were similar in both groups. No significant prevalence of cerebrovascular lesions was found in the FTLD brains.
Strengths of the study: Neuropathological validated FTLD diagnosis.
Weakness of the study: Small sample sizes in both cases and controls.

Borroni et al (2007) aimed to assess the association between education and FTD (56).
Design: Case-control study.
Cases and controls: 117 cases with FTD was compared with a control group of 400 patients with Alzheimer's disease, a control group with 55 patients with progressive supranuclear palsy (PSP), and a control group of 55 patients with corticobasal degeneration (CBD). The cases and controls were selected from two different medical centers between 1993 and 2007.
Data on dementia diagnosis: Cases and controls underwent somatic, neurological, and laboratory examination and evaluation. The dementia diagnoses were based on diagnostic criteria.
Risk factors: The following risk factors were assessed: age, education, gender, family history of dementia, cardiomyopathy, hypertension, hypercholesterolemia, diabetes, and apolipoprotein 4.
Data on risk factors: Cases and controls underwent somatic, neurological, and laboratory examination and evaluation.

Findings: The patients with FTD had a lower prevalence of cardiomyopathy than in patients with AD and a lower prevalence of hypertension than in PSP. In terms of education, the study found that the cases of FTD had higher levels of education than the control groups of AD, PSP, and CBD. The study found no associations between FTD and the modifiable variables in the adjusted variables, which may be due to the lack of longitudinal design.
Strengths of the study: Validated dementia diagnoses
Weakness of the study: The population of FTD cases and the control groups of PSP and CBD were small, and the study does not have a cognitively healthy control group. The FTD cases were also, on average, younger at disease onset than the control groups. The differences in age may be a bias, as higher levels of education are more common in younger persons.

Rosso et al (2003) aimed to assess medical and environmental risk factors for sporadic frontotemporal dementia (16).
Design: Retrospective case-control study.
Cases and controls: 80 cases with sporadic FTD were compared to a control group of 124 patients without cognitive impairment or dementia.
Data on dementia diagnosis: Cases were identified through a nationwide study on FTD which took place between 1994-2002. The FTD diagnoses were based on international clinical criteria, and cases were considered to have a sporadic FTD if there was no dementia in the first-degree relatives nor any tau mutations identified.
Risk factors: The risk factors investigated were hypertension, diabetes mellitus, high cholesterol, myocardial infarction, stroke, meningitis/encephalitis, seizures, head trauma, head trauma with loss of consciousness, thyroid disease, headache, migraine, herpes zoster, cold sores, severe dementia, level of education (low, intermediate, high), smoking (never, less than 20 pack-years, more than 20 pack-years), alcohol consumption (less than a drink/day, 1-3 drinks/day, more than 3 drinks/day), and exposure to chemicals, pesticides or insecticides.
Data on risk factors: The information on risk factors was collected from a surrogate informant and was considered as a risk factor if it preceded the date of the onset of dementia. Head trauma was considered if it was followed by nausea, severe headache, blurred or double vision, vertigo, amnesia, or loss of consciousness, and severe head trauma if the trauma was followed by loss of consciousness. Thyroid problems were considered if confirmed by a general practitioner.
Findings: The cases of FTD had a higher prevalence of head injury that the control group. In this study, no significant associations were found between smoking, hypertension, diabetes

mellitus, high cholesterol, myocardial infarction, or stroke and FTD.
Strengths of the study: Validated dementia diagnoses**.**
Weakness of the study: This study lacks a longitudinal design. The association between FTD and head injury may be under influence by recall bias, as this information was collected from surrogate informants. Also, the study has a small sample size.

Deutsch et al (2015) aimed to assess interactions between traumatic brain injury and frontotemporal degeneration (57).
Design: A case-control study.
Cases and controls: 1016 cases with FTD spectrum disease (behavioral variant FTD, progressive non-fluent aphasia, and semantic dementia) was compared with a control group of 2015 patients with no cognitive impairments.
Data on dementia diagnoses: The behavioral variant of FTD was diagnosed using the Neary criteria. Progressive non-fluent aphasia and semantic dementia were diagnosed using the Mesulam criteria. The cases were identified through a large, multi-center database that includes clinical, cognitive, behavioral, and functional assessments.
Risk factors: The study includes assessments for three levels of traumatic brain injury. Demographic data included gender, age, and education.
Data on risk factors: The data on risk factors was collected from the National Alzheimer's Coordinating Center Uniform Data Set.
Findings: The findings in the study indicated that traumatic brain injury with extended loss of consciousness may increase risk for FTD by 67%.
Strengths of the study: This study has a large population of FTD cases with validated FTD diagnoses and a large control group with cognitively healthy individuals.
Weakness of the study: There is a lack of longitudinal design which makes it difficult to consider if brain injury is a risk factor or a potential consequence of the disease. The reporting of traumatic brain injury was retrospective and could therefore be influenced by recall-bias. This study also lacks important control variables, such as disease related variables and lifestyle related variables.

A study by Miller et al (2013) aimed to assess the association between TDP-43 frontotemporal degeneration and autoimmune disease (58). TDP-43 is a major pathological protein in the frontotemporal lobar degeneration with ubiquitinated inclusions.
Design: Case-control study.
Cases and controls: 129 cases with the semantic variant of primary progressive aphasia

(svPPA) were compared to one control group of 39 patients who were progranulin mutation carriers (PGRN), one control group with 186 patients with normal cognition (NC), and one control group of 158 patients with Alzheimer's disease (AD).
Data on dementia diagnoses: The cases and the control group with Alzheimer's disease were selected from two different medical centers and diagnoses were set based on diagnostic criteria. The control group with normal cognitive function was selected from a study about normal aging. The cases and the control groups were matched for gender, education, and race.
Data on risk factors: The data on autoimmune disease was selected from the medical records of the patients.
Findings: In this study a higher prevalence of autoimmune conditions was observed in svPPA and PGRN carriers compared to the control group.
Strengths of the study: Validated diagnosis of svPPA and AD.
Weakness of the study: The groups of cases and controls are small. The data on autoimmune disease was collected retrospectively from medical records and not laboratory-based evaluations of autoimmune disease. This may have resulted in an underrepresentation of the prevalence of autoimmune disease in the sample. Also, this study did not include any control variables of other diseases or risk factors.

Torralva et al (2015) aimed to assess the role of brain infarcts in behavioral variant frontotemporal dementia (59).
Design: Case-control study.
Cases and controls: 62 patients with V-bvFTD (patients with behavioral variant of FTD and coexistent cerebrovascular disease) were compared to 329 patients with NV-bvFTD (patients with behavioral variant of FTD and no cerebrovascular disease).
Data on dementia diagnoses: The FTD cases were included from the National Alzheimer's Coordination Centre Database**.** Patients with aphasic variants of FTD were excluded.
Risk factors: Mean age at onset of cognitive decline, mean age at last assessment, mean age at death, years of education, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking habits, atrial fibrillation, coronary artery disease, congestive heart failure, prior TIA (transient ischemic attack), prior stroke.
Data on risk factors: The data was collected from the National Alzheimer's Coordination Center and obtained from the treating physician.
Findings: The patients in the V-bvFTD group were characterized by less severe neurodegeneration, were older at the onset of cognitive decline and death, and were more

likely to have hypertension or history of stroke. They had similar cognitive profiles to the NV-bvFTD group.

Strengths of the study: This study gives information about the possible co-existence of FTD and cerebrovascular disease, which has not been sufficiently explored. The study used clinical FTD diagnoses.

Weakness of the study: The population of patients with V-bvFTD is small. The authors list some limitations to the cognitive and functional assessments. The study examined the role of brain infarcts in bv-FTD and did not use a control group of other dementia patients nor a healthy control group. The study does not give any information about risk factors for FTD, but information about coexistence of cerebrovascular disease and FTD.

1.3.2 Treatment

No cure currently exists for FTD (23, 60), and the only treatment available is selective serotonin reuptake inhibitors (SSRIs) to relieve the symptoms (30). So far, the most important intervention in FTD is support for the patients, families, and caregivers (60).

1.3.3 Phenotypic groups

FTD can be divided into two phenotypic groups based on changes in language or behavior: the behavioral variant of FTD and the language variant of FTD. Clinically and pathologically, FTD can also overlap with motor neuron disease, corticobasal degeneration, or progressive supranuclear palsy (8, 61-63) (Textbox 3).

Textbox 3: Phenotypic groups of FTD and overlaps with other neurodegenerative diseases

Frontotemporal dementia		
Behavioral variant FTD	**Language Variant FTD** (Primary progressive aphasia)	**Overlaps with other neurodegenerative disease**
	⬇	⬇
	Non-fluent variant (progressive non-fluent aphasia)	Behavioral variant of FTD with motor neuron disease
	Semantic variant (Semantic dementia)	Corticobasal degeneration
	Logopenic variant (Logopenic aphasia)	Progressive supranuclear palsy

The behavioral variant of FTD is characterized by focal and prominent frontal atrophy, and the symptoms include changes in personality and behavior (45, 62). The most common early symptoms are personality changes, disinhibition, and apathy (45). Changes in personality and behavior can result in socially inappropriate behavior and impulsive or careless actions (45). The patients are often misdiagnosed with non-dementia disorders, such as psychiatric disease, alcohol/substance abuse, neurological disorders, and cerebral vascular disease (30, 31).

The language variant of FTD is known as primary progressive aphasia and is characterized by bilateral anterior temporal lobe atrophy (8). The language variant consists of three subtypes: a non-fluent variant, a semantic variant, and logopenic aphasia (8, 14, 30).

The non-fluent variant is characterized by effortful speech and word-finding problems, as well as labored, slow, slurred, and choppy speech as the disease progresses (23).

The semantic variant is characterized by difficulties in understanding the meaning of words, and the patients have anomia for places, people, and objects. The patients experience word-finding difficulties and impaired word comprehension but retain correct grammar and fluent speech (45).

The logopenic variant is characterized by difficulties in using the correct words (44). The patients have slow, labored, halting speech production and agrammatism. They often make speech sound errors and have problems in understanding sentences (45).

1.3.4 Epidemiology

Today, FTD is considered to be the second most common degenerative disease causing dementia in younger adults (9, 14, 64). FTD is considered as an umbrella term for neurodegenerative disorders characterized by atrophy of the frontal and temporal lobes of the brain (51, 59, 65).

The age at onset is typically in the 50s or 60s (66), but some cases have been reported in youth (67), and others in later life (68). The average age of diagnosis is 57 years old (14). Determining the prevalence of FTD cases in the world is challenging, mainly due to underdiagnosis (8, 69).

Recent studies estimate the incidence of FTD to be 1.61 to 4.1 cases per 100,000 people annually (23, 70). A systematic review on prevalence of FTD shows that men and women are equally affected, and that the behavioral variant of FTD was diagnosed four times more frequently than the language variant FTD diagnosis (71).

Another study suggests that the behavioral variant of FTD constitutes 60% of FTD cases, while the language variant of FTD constitutes remainder (14).

1.3.5 Diagnostic criteria

The diagnostic criteria for FTD was last proposed in 2011 by the international consortium with guidelines for both behavioral and language variants of FTD (72). A full neurological examination with brain imaging is recommended (64).

One challenge in diagnosing FTD is that the symptoms are similar to those of psychiatric disorders (45). Other challenges are lack of insight (in the person suffering from FTD) and gradual onset of disease (73). Therefore, it is necessary to obtain a history of behavioral, cognitive, or functional decline from a reliable informant (64).

1.3.6 Family caregivers

Family members are most often given the responsibility of caregiving for dementia patients (74). Being a family caregiver for someone with dementia may be a physical, psychological, emotional, and economical burden (75).

Being a family caregiver for someone suffering from FTD dementia may be particularly challenging and burdensome, due to the behavioral and personality changes, young onset, and delay in diagnosis (8, 31, 76-78).

Caring for a loved one with dementia is demanding and has an impact on spousal relationships as a result of the changes in the person with dementia, changes in shared identities, interaction, and future life plans (79). In FTD, the person affected is more likely to lose the abilities of emotional connection, empathy, self-awareness, and social appropriateness. This may be particularly damaging to the marital bond (80, 81).

Another challenge for family caregivers of persons with FTD is a lack of follow-up care provided by health care services (82, 83). Family caregivers are often frustrated, as little is known about FTD, and express a need for more research and development of support and facilities to provide competent care (84).

FTD is a rare disease, and lack of knowledge about symptoms, the course of the disease, and the burden on family caregivers is common (82). Furthermore, the lack of knowledge about FTD and its symptoms in the general public leads to less understanding and support for family caregivers (83). More patients with FTD are admitted to nursing homes after the FTD diagnosis compared to patients with early onset AD (82). This is probably associated with the severity of symptoms in FTD, such as behavioral and personality changes (82). Caregiving for patients with FTD at nursing home units also often presents significant challenges for the nursing staff (85).

1.4 Risk factors

1.4.1 Risk

The word “risk” is widely used and may be readily understood as a cause of disease (18). The definition of risk is the probability of an event, e.g. that an individual will become ill or die during a specified period of time or by certain age (86, 87). Risk also encompasses a variety of measures of the probability of an unfavorable outcome (87).

1.4.2 Risk factors

In epidemiology, the term "risk factors" is often used to indicate factors associated with given outcomes (86). A risk factor may be defined as an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the bases of epidemiological evidence, is known to be associated with health related condition(s) considered important to prevent (87). Some risk factors are potentially modifiable, such as diet, lifestyle, and cardiovascular disease. Other risk factors, such as genetics and age, are considered unmodifiable (17). Risk factors may also be called exposure variables. Risk factors should not be confused with causes. A risk factor provides a statistical possibility of prevention but is not necessarily a cause.

1.4.3 Causative factors

A cause or causative factor of a disease occurrence is defined as a condition, event, or characteristic without which the disease would not have occurred (86). A causative factor is not a complete causal mechanism. A complete causal mechanism, also called a sufficient cause, is defined as a minimal set of conditions and events that are sufficient for the outcome to occur (86). The determination of if a given relation is causal or not is called causal inference (18). The major criteria used today for determination of causal inference are strength of association, time sequence, and consistency (50). Hills criteria of causation is a commonly used set of criteria (86). Hill suggested that strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence, and analogy should be considered in order to distinguish causal from non-causal associations (86).

1.4.4 Associations

Epidemiologic studies often aim to study the association between an exposure variable and an outcome (50). An example might be obesity (exposure) and diabetes (outcome). In epidemiologic studies, associations may be categorized as disease frequencies (occurrence) and impact or importance. Relative risk or odds ratio is often used in this manner (50). The measure of association between an exposure variable and an outcome gives the strength and direction of the association between the exposure and the outcome by using comparing groups (50). An association between an exposure and an outcome is a general relationship. It shows that one variable provides information about another variable (88).

1.5 Anxiety and depression as risk factor for dementia

Anxiety and depression disorders are highly prevalent in the population (89, 90). Symptoms range from mild to severe and duration from months to years. Anxiety and depression differ from the feelings of stress, fear, or sadness that anyone can experience occasionally (91). An anxiety or depression diagnosis requires clinical assessments (92).

Anxiety disorders include generalized anxiety disorder (GAD), panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). These disorders are characterized by feelings of anxiety and fear (91). Anxiety is a highly prevalent psychiatric condition in late life (93, 94).

Several studies have found anxiety to be a risk factor for AD and dementia in general (95-101); a few hypotheses have been suggested to explain the association between anxiety and dementia.

One hypothesis is that apolipoprotein E may be linked to anxiety as well as dementia (102), and neuropeptides and the hypothalamic-pituitary-adrenal axis may be involved (101). A mediating factor could be anxiety treatment by benzodiazepines. Some studies have found benzodiazepines as a risk factor for AD (103).

A recent review found anxiety as a risk factor for both AD and vascular dementia (104). This study also offered a hypothesis regarding the association between anxiety and dementia. Anxiety is characterized by neurotoxic distress, which may lead to alterations in glucocorticoids that may affect the neurons. In addition, anxiety may lead to avoidance behavior and an inactive lifestyle, which are known to be risk factors for dementia (104).

Depressive disorder includes two main sub-categories: major depressive disorder/depressive episode and dysthymia. Both of these disorders are characterized by sadness, loss of interest, feelings of low self-worth or guilt, disturbance in sleep or appetite, tiredness, and poor concentration (91). Depression is common in late life (105, 106) and has been found to be a risk factor for dementia in several studies (39, 107-111).

Several hypotheses have suggested an association between depression and dementia, which have been discussed in a review published in 2011 (112). Vascular disease is one link between depression and dementia. Depression is associated with life style habits such as

smoking and inactivity, which again may lead to obesity and metabolic syndrome (112). Moreover, depression increases the risk for myocardial infarction and stroke (112).

Another proposed hypothesis for the association between depression and dementia is the occurrence of alterations in glucocorticoids. Depression may lead to increased glucocorticoid production, which may damage the hippocampus. Atrophy of the hippocampus is an early brain change in AD, and reduced hippocampus volume has also been found in individuals with depression (112).

Amyloid plaques are a characteristic finding present in AD patients. Some studies have shown that AD patients with depression have a larger number of plaques in the hippocampus compared with AD patients without depression. It has also been suggested that the increased number of plaques are due to a stress response associated with depression and glucocorticoids (112).

Some studies have suggested that chronic inflammation is a link between depression and dementia. Increased cytokine levels found in patients with depression may indirectly lead to increased pro-inflammatory changes in the central nervous system (CNS) and dementia. Pro-inflammatory cytokines also interfere with serotonin metabolism (112).

Brain-derived neurotrophic factor is necessary for neuronal health; its deterioration has been detected in both individuals with depression AD (112).

1.6 Smoking and obesity as risk factors for dementia

Smoking and obesity are two of the five leading global risks for mortality (113). More than seven million people die from tobacco use each year (114). Obesity is increasing worldwide due to decreasing physical activity and changes in diet (113). Several studies have stated obesity and smoking as risk factors for dementia (3, 41-43, 95, 115-118).

A healthy heart ensures that enough blood is pumped to the brain, and healthy blood vessels enable the blood to reach the brain. Cardiovascular disease is associated with the risk of development of dementia (28). It has been hypothesized that use of tobacco can lead to dementia indirectly through cardiovascular disease, stroke, heart disease, increased plasma homocysteine, cerebrovascular disease, atherosclerosis, and oxidative stress (118). Increased

plasma homocysteine is associated with atherosclerosis, cardiovascular disease, and stroke (119). In addition, smoke contains several toxic chemicals known to damage brain cells and, in turn, increase the risk of stroke (120).

Obesity is linked with an increased risk of dementia (39, 41, 121) through mechanisms such as diabetes, cardiovascular disease, increased inflammation, cardiovascular disease, and higher levels of cytokines (121). It has been associated with decreased brain volume and grey matter atrophy in the temporal, frontal, and occipital cortices; hippocampus; thalamus; and midbrain (122). Obesity has also been associated with decreased blood flow in the prefrontal cortex of the brain and an increase in brain age (122).

2 Aims of the thesis

The overall literature review of the thesis shows that there is a lack of studies on family caregivers' experiences regarding the early stage of FTD and a lack of studies on modifiable risk factors for FTD. These gaps in knowledge may contribute to delays in FTD diagnoses and that no prevention strategies exist for FTD today. The aim of the present thesis was contribution to the gaps in knowledge revealed in the literature review. The studies in the thesis would add new information about the challenges in timely FTD diagnosis, new information about the research field of moddifiable risk factors for FTD and new information about anxiety, depression, smoking and obesity as risk factors for FTD.

The rationale of the studies in the thesis was to:

- Obtain an overview of the number of studies that had assessed modifiable risk factors for FTD, and determine if any modifiable risk factors had been identified. Additionaly,

- Study the family caregiver's experiences regarding the pre-diagnostic stage of FTD, and to illuminate some of the challenges related to establishing an FTD diagnosis.

- Study anxiety, depression, smoking, and obesity as risk factors for FTD in comparison with risk factors for AD and cognitively healthy individuals.

3 Overall ethical reflection

The ethics of the studies are discussed separately under the sections 5.6 and 6.2.7. In addition, there is a need for an overall ethical reflection of the thesis.

Today's research ethics are based on the Nuremberg Code from 1946. The Nuremberg Code has subsequently been continued in the Declaration of Helsinki. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects. All researchers are obliged to follow the ethical principles in this declaration. Every research project must present a project protocol with statements of the ethical considerations and how the principles in the declaration have been addressed. The research protocol then has to be submitted to the Research Ethics Committees for consideration, comment, guidance, and approval (123). In the Nord-Trøndelag Hospital Trust, every research project has to be approved by the Department of Research before being submitted for consideration to the Research Ethics Committees. The Department of Research ensures that medical and health-related research is carried out properly and in accordance with the legislation through a Data Access Committee. The PhD project protocol was first approved by the Data Access Committee, then subsequently approved by the Research Ethic Committees.

The PhD project use data from the Nord-Trøndelag Health Studies (HUNT) and the Dementia Register in the Nord-Trøndelag Hospital Trust. The HUNT Study is approved by the Data Inspectorate of Norway and recommended by the Regional Ethic Committee. All data from HUNT is treated according to the guidelines of the Data Inspectorate(124) . The Dementia Register in the Nord-Trøndelag Hospital Trust (The project "Health and Memory Study") also received approval from the Research Ethics Committee (125).

There are numerous ethical issues when it comes to research on dementia, especially since the nature of the disease affects the person’s cognitive abilities and possibilities for independence. I chose to reflect upon ethical issues that appeared during the work of the thesis.

In study 2, there was focus on the symptoms of FTD such as changes in behavior and personality in the published article. Also, these changes are described as challenging and burdensome for family caregivers. I had considered if this could cause stigma related to FTD or make persons with FTD seem dangerous. I have strived to have modest and adequate descriptions of the symptoms of FTD and the burden this constitutes for the family caregivers. Also, I explained the reason why these symptoms occur: the disease affects the temporal and/or the frontal lobes in the brain whom have important functions regarding personality and behavior. Hopefully, increasing the knowledge of the cause of the symptoms will work against any stigma. The aim of the study and the article was to increase knowledge on FTD, the symptoms of FTD, and the experiences of family caregivers in the pre-diagnostic stage of FTD.

In study 2, I have argued that it is important to achieve an early FTD diagnosis. This raises an ethical question that has been debated in the field of dementia: to know or not to know? Some argue that there are few good reasons for early AD diagnosis if there is a lack of disease modifying therapy. Also, there is the possibility that an early dementia diagnosis may lead to depressive or even suicidal reactions in the patient (126). The same ethical issues are present regarding early FTD diagnosis, as no medical treatment currently exists. However, an accurate diagnosis will prevent incorrect medical treatment and increase family caregivers' opportunities to seek supportive resources.

The informants in study 2 received a detailed informant letter about the study before giving their consent. The informant letter described the background and rationale for the study, possible advantages and disadvantages, and roles of the researcher and informants. They were aware of that they would be asked questions about their loved ones and that this could have emotional affects. As I developed the interview guide, I strived to show respect for their privacy when forming the questions. Still, it sometimes felt as if it was devastating for the informants during the interviews. However, all informants expressed that they were okay after the interviews. They had the opportunity to contact me after the interviews if they needed to, which none of them did. All the informants expressed that it felt important for them to participate in research on FTD.

As I worked with the material from the interviews, I recognized that some information could be recognized by readers from the same living area. Some of the behavior in social settings

described by the informants stood out and was probably recognized by others nearby. To secure confidentiality, I chose not to quote or refer to these situations.

Studies 3 and 4 are epidemiological case-control studies on modifiable risk factors for FTD. In the thesis, I argued that detection of modifiable risk factors for dementia is crucial to finding prevention strategies in the future. Research on modifiable risk factors that uncovers causal relationships between risk factors and dementia may result in a lack of sympathy towards people with dementia; they may be blamed for having dementia. Also, people may be overly optimistic about their chances of preventing dementia (127). In the articles from studies 3 and 4, I have stated both strengths and limitations of the study. Also, I have made clear that the findings show suggested associations (not causal relationships) and that more research studies need to be performed to provide further enlightenment on the findings.

4 Study 1

4.1 Aim

To obtain an overview of the number of studies that assessed modifiable risk factors for FTD, and if any modifiable risk factors have been previously identified.

4.2 Method

A systematic literature review was performed in accordance with the PRISMA criteria (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (24) and the guidelines of the journal "Tidsskrift Den Norske Legeforening". According to the PRISMA criteria, a systematic review has a clearly formulated question (24).

The question for study 1 was, "How many studies have assessed modifiable risk factors for frontotemporal dementia, and does the research field have an evidence base for a clinical recommendation on how to reduce the risk of frontotemporal dementia?"

A systematic search was set up in cooperation with a librarian at the Namsos Hospital library in June 2016 in the databases PsychInfo, Embase, PubMed, and Cochrane. The MeSH terms and keywords used were, "frontotemporal degeneration," "frontotemporal dementia," "frontotemporal lobar degeneration," "dementia," and "risk factors."

The search was limited to articles published in the period 1 January 2005 to 24 January 2017, and filtered by the following languages: Norwegian, Swedish, Danish, and English. The search was an auto alert search, which gave updated search results once weekly.

The inclusion criteria for the review were review article or original studies with data on modifiable risk factors for frontotemporal dementia. Exclusion criteria for the review were studies of non-modifiable risk factors for frontotemporal dementia, case reports, opinion pieces, and conference proceedings.

The literature search resulted in 137 articles. Of these, 101 articles were excluded because the titles revealed that they were not about modifiable risk factors.

A total of 36 articles were read in full text and 25 of these were excluded because they were not related to modifiable risk factors. Finally, a total of 11 articles were included in the study. In addition, an article from the reference list of one of the 11 was included. This resulted in a total of 12 articles with data on modifiable risk factors for frontotemporal dementia.

The review was written in line with the guidelines of systematic review in the "Tidsskrift for Den Norske Legeforening."

5 Study 2

5.1 Aim

To illuminate the experiences of family caregivers of patients in the early stage of FTD.

5.2 Method

5.2.1 Qualitative methods

To investigate the experiences of family caregivers of the pre-diagnostic stage of frontotemporal dementia, I performed narrative interviews with family caregivers. I was not only looking for the earliest symptoms of FTD, but also family caregivers' experiences of these symptoms.

A qualitative phenomenological-hermeneutic method was appropriate for this study. Qualitative methods cover a wide range of methods in which in-depth interviews and focus groups are common (128).

5.3 Design

5.3.1 Phenomenology and hermeneutics

Phenomenology is a philosophical tradition developed by Husserl and Heidegger and an approach to explore and understand people's everyday experiences (21). Interpretive phenomenology or hermeneutics strives to interpret and understand the human experience (21). Gadamer, an interpretive phenomenologist, described the interpretive process as a circular process, also known as the hermeneutic circle, where the researcher continually questions the meaning of the text (21).

I decided that a qualitative method, with a phenomenological approach and hermeneutic interpretation was the most appropriate method to use in my study.

5.3.2 Semi-structured interview

To cover the aim of the study, I created a semi-structured interview guide with the following questions:

- "Could you please tell me about the first time you experienced that your loved one has changed and what it meant to you?"
- "Could you please describe the changes?"
- "Could you please tell me more about your experience of the changes?"
- "Could you please tell me what the changes meant to you?"

5.4 Participants and interviews

The participants were recruited in cooperation with the medical staff at two hospitals' psycho-geriatric units and one hospital's neurological unit. The inclusion criterion for the participants was a close relationship with a person during the pre-diagnostic stage of FTD and subsequent diagnosis of the person with FTD. After approximately six months, 16 people agreed to join the study, of whom 14 participated in the study.

An informant letter was handed out following the informant consent to the potential participants. The participants were contacted by phone after their consent letters were received.

The arrangements for the interviews were made according to the participants' wishes. One interview took place at an office at a hospital, and one took place at a conference room at a hotel, but the rest of the interviews took place in the homes of the participants. All interviews were recorded and transcribed verbatim.

There was a variation in years between observation of the earliest symptoms of FTD and actual FTD diagnosis (0 to 12 years). One participant's loved one was diagnosed with FTD the same year as the first symptoms were observed, one participant's loved one was diagnosed one year after the first symptoms were observed, and the rest had loved ones who were diagnosed 2 or more years after the first symptoms were observed (Figure 4). There was also a variation in age at which the earliest FTD symptoms were observed (45–68 years). The participants had different roles in the relationships with their loved ones. Some were spouses, some were daughters, siblings, or close friends/earlier cohabitants. Some of the participants were still living with their loved one, some of the participants had experienced the death of their loved ones, and, in some cases, the loved one had moved to an institution. All the participants were in different stages of mourning during the interviews.

Table 1: The participants and their loved ones

Nr	**Relationship to person with FTD**	**Gender of person with FTD**	**Age at earliest FTD symptoms observed**	**Age at FTD diagnosis**	**Years between observation of earliest symptom of FTD and FTD diagnosis**
1	Daughter	M	55	67	12
2	Husband	F	45	47	2
3	Wife	M	65	69	4
4	Husband	F	67	67	0
5	Husband	F	64	67	3
6	Husband	F	61	64	3
7	Husband	F	45	55	10
8	Brother	F	65	70	5
9	Daughter	M	62	63	1
10	Wife	M	64	68	4
11	Wife	M	57	67	10
12	Close friend/former cohabitant	M	68	76	8
13	Daughter	M	66	70	4
14	Daughter	F	60	68	8

Descriptions of participants' relationships to the persons with FTD. Descriptions of the loved ones with FTD: gender, age at earliest FTD symptoms, age at FTD diagnosis, and years between first symptoms and FTD diagnosis.

5.5 Text analysis

The analyses and interpretations in this study were inspired by the proposal of Fleming et al. (2003) (129). In their article, the authors proposed a five-step approach to conduct nursing research in the Gadamerian hermeneutic tradition. The proposal of Fleming et al. (2003) is built on the most recent version of "Wahrheit und Methode" (Truth and Method), Gadamer (1990) (129).

According to Gadamer (1993), it is not possible to step outside of history and look back at the past objectively. Understanding is only possible with historical awareness, which means that everyone has a preunderstanding of the topic in question. The preunderstanding must be recognized, or else there is a risk that understanding will fail or meaning will be misjudged. The preunderstandings of the phenomenon should be reflected upon during the process of gaining understanding (129).

The interviews were transcribed into text, and the whole text was read by all of the authors. In the first step, I reflected upon my preunderstanding of the research question: How do family caregivers experience the pre-diagnostic stage of FTD? My preunderstanding of the topic was that the family caregivers experience changes in their loved one due to FTD many years before the FTD diagnosis.

In the next step, all the authors separately read the interviews as a whole text. Thereafter, I reviewed and wrote the fundamental meaning of the text as a whole, and this was read and reviewed by all the authors. In the next step, I gained an overall understanding of each text unit.

Every sentence or section was investigated to determine its meaning in the context of the research question. The themes were reflected upon in light of my pre-understanding. Thereafter, every section or sentence was related to the meaning of the whole text.
In the final step, I identified the passages that seemed to be representative of the shared understandings of the participants and the researcher. This multistep process was carried out several times during the analysis. The participants' perspectives were represented in the text as clearly and closely as possible, and direct quotations were included.

5.6 Ethics

The participants were carefully informed in the informant letter that the interviews could trigger strong emotions both during and after the interview. They were told to contact the main researcher if they needed support. The study was approved from the Regional Ethical Committee in 2015 (REK), the Norwegian ethics committee.

6 Study 3 and Study 4

Studies 3 and 4 are both epidemiological studies and have a longitudinal design. The studies used data from the HUNT studies and the Dementia Register of Nord-Trøndelag. Both are case-control studies and use multivariate regression analyses.

I have described the rationale of the control groups, the HUNT studies, the Dementia Register in Nord-Trøndelag, the cognitively healthy control group and the rationale of the risk factors in section 6.1: "Background and material". I have described epidemiology, quantitative research methods, longitudinal studies, case-control studies, nested case-control studies, logistic regression analyses, and ethics in section 6.2: "Method." Study population, covariates, and variables are described in section 7: "Study 3" and section 8: "Study 4".

6.1 Background and material

6.1.2 The rationale of the control groups

FTD and AD have significant differences regarding pathology and symptoms. FTD also affects younger persons more often than AD. Nonetheless, both FTD and AD belong under the umbrella category of dementia and are comparable diseases in research. Using a control group with AD gave us the possibility to investigate risk factors between two comparable diseases. The similarities between FTD and AD present a challenge when separating the diseases, particularly late in the AD disease process. Using a control group of cognitively healthy individuals gave us the ability to investigate risk factors between FTD, AD, and cognitively healthy individuals.

6.1.3 The Nord-Trøndelag Health Studies (HUNT)

All inhabitants of Nord-Trøndelag County in Norway aged 20 years or older were invited to participate in four surveys, HUNT1 (1984-86), HUNT2 (1995-97), HUNT3 (2006-08), and HUNT4 (2017-2019). The HUNT4 study is not discussed further in the thesis.

In HUNT1, HUNT2, and HUNT3, the participants were asked to complete two extensive questionnaires, including more than 200 health-related items. The participants were also invited to a brief medical examination (130).

The aim of the HUNT1 study was primarily to assess hypertension, diabetes, tuberculosis, and quality of life (130). The participants were asked to answer questionnaires with self-reported health, quality of life, illnesses, diseases, behavioral risk factors, and socio-economic status. Weight, height, blood pressure, and heart rate were measured. Chest x-ray images were obtained to screen for tuberculosis. Capillary non-fasting blood glucose levels were also analyzed (130).

Since HUNT1, the scope of the HUNT studies has expanded (130). HUNT2 was a follow up of HUNT1, but included a wider range of topics in addition to those in HUNT1(124) . This included disease-specific questionnaires for hypertension, diabetes, and lung diseases; measurements of waist and hip circumference; and venous blood samples analyses for cholesterol, triglycerides, glucose, serum ferritin, and creatinine. For sub-groups in HUNT2, spirometry, forearm bone mineral density, and vision were measured. In the venous blood samples for sub-groups, thyroid-stimulating hormone, calcium, and parathyroid hormone were measured. DNA was also extracted from the blood and stored. Anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS) (124, 130).

The studies in this thesis have not used data from the HUNT3 study. The details of measurements in HUNT3 are, therefore, not described.

6.1.4 The Dementia Register in Nord-Trøndelag

The Dementia Register of Nord-Trøndelag Health Trust consists of data collected from two different registers: the nursing home dementia register and the hospital dementia register.

The hospital dementia register includes data on dementia diagnoses collected retrospectively (1995-2010) and prospectively (2010-2017) from two hospitals, the Namsos Hospital and the Levanger Hospital (125). Diagnoses were determined according to the national and international guidelines by specialists in geriatric and psychogeriatric medicine and based on

patient history, caregiver history, clinical examinations, neuropsychological assessments, blood samples, and brain imaging (125).

The nursing home dementia register includes data on dementia diagnoses collected from nursing homes in Nord-Trøndelag during 2010-2011. Nine registered nurses with appropriate clinical experience performed the assessments using a standardized interview with the patients and their closes relatives. Two physicians with wide clinical and research experience independently diagnosed mild cognitive impairment (MCI), dementia syndromes, and dementia subtypes using all available information. If there was a disagreement about a dementia diagnosis, a third expert was consulted. The same criteria for etiological dementia diagnoses were used as in the hospital dementia panel (125).

6.1.5 The cognitively healthy control group

The cognitively healthy control group (CH) in Studies 3 and 4 was selected from a follow-up project on memory and intelligence after HUNT3 between 2010 and 2011. The aim of this follow-up project was originally to find a healthy Norwegian sample for testing translations of the Wechsler Memory Scale III and the Wechsler Intelligence Scale III. The HUNT research center extracted potential participants from the HUNT database. Before testing, the participants were interviewed about current diseases that would make them unsuitable for inclusion in the study. The inclusion criteria for the sample were: age 55-89 years, normal hearing and vision, absence of mental or medical diseases affection cognition (based on self-assessment), a general medical checkup in HUNT3, and adequate physical functioning to meet testing requirements. The individuals in the sample were recruited from the county of Nord-Trøndelag (131).

The sample consist of 122 individuals aged 55-89 years. All of the individuals have completed medical testing and questionnaires in the HUNT3 study and consented to participate in a comprehensive study of cognitive function. The participants had 10.7 years of education on average and 52.5% were women (131).

6.1.6 The rationale of risk factors

Our systematic review in Study 1 revealed that very few studies have been performed evaluating modifiable risk factors for FTD; the studies performed have different designs and most have small sample sizes. Additionally, the findings regarding cardiovascular risk factors were conflicting. One study found significant associations between FTD and diabetes. Three studies have shown that head injury increases the risk of developing FTD, but two of these

studies also had small sample sizes and all used different definitions of head injury. In conclusion, the current evidence in literature is too narrow to draw any conclusions regarding modifiable risk factors on FTD.

Study 3

In our project protocol, our original plan for Study 3 was to study anxiety and depression as risk factors for FTD. FTD often presents with psychiatric symptoms, and we, therefore, found it interesting to study anxiety and depression as risk factors for FTD. Depression is also a known risk factor for AD. No other studies have assessed anxiety or depression as risk factors for FTD.

We planned to use data on anxiety and depression (HADS) from HUNT2. The data on anxiety and depression from HADS in HUNT2 are considered valid data on anxiety and depression. We wanted to use age, gender, education, and morbidity as control variables.

As we started to work on the analyses, we discovered that the information regarding education was missing in 25.4% of cases. There were 24 cases in the FTD population, 66 cases in the AD control group, and 7 cases in the cognitively health (CH) control group missing education information, respectively. As a result, we chose to not use education as a control variable. We had also wanted to use alcohol as a control variable. We discovered that this variable was missing in 48.2% of cases; 33 cases in the FTD population, 243 cases in the AD control group, and 16 cases in the CH control group were missing this information, respectively. Had included the education variable, the large number of missing cases would have reduced the size of both cases and controls significantly, particularly in the FTD population. As such, we chose not to use alcohol as a control variable either.

We decided to use anxiety and depression from HUNT2 as risk factors, and sex, mean age at participation in HUNT2, mean age at dementia diagnosis, heart disease, diabetes, hypertension, metabolic disease, and obesity as control variables.

Study 4

In our project protocol, our original plan for Study 4 was to perform a study on lifestyle habits (smoking, use of alcohol, diet, physical activity), diabetes, cardiovascular variables (obesity, high blood pressure, heart disease, high cholesterol), and education as risk factors for FTD. We planned to use data from the HUNT1 Study. However, during the research process, our plans for the study changed.

When applying for data, it was recommended by the data owners to choose two variables rather than including several. We then chose to apply for data on smoking and diabetes as risk factors. Our rationale for these risk factors was that smoking could influence the brain through vascular conditions and toxicity, and that changes in glucose metabolism could affect the brain. Smoking and obesity are also well known risk factors for other types of dementia.

As we started to work on the analyses, we discovered that very few participants had reported diabetes. In the population with FTD, only one participant had reported diabetes. Only 6 participants in the AD control group and 2 participants in the CH control group had reported diabetes. The few reporting cases with diabetes would have been insufficient to detect associations. Therefore, we chose to use diabetes as a control variable instead of an effect variable.

Another variable that presented some challenges was participants' education level. We found that this variable was missing in 18% of cases. In the population with FTD, there were cases 13 missing the data. There were 85 cases in the AD control group and 26 cases in the CH control group missing education data. Therefore, we chose not to use education level variable.

We decided to use smoking and obesity as risk factors, and sex, mean age at participation in HUNT1, mean age at dementia diagnosis, heart disease, diabetes, and hypertension as control variables.

6.2 Method

6.2.1 Epidemiology

Epidemiology is traditionally seen as a quantitative discipline that investigates possible associations between particular factors and risk for a disease at a group level. Another role of epidemiology is to describe variations in morbidity or disease development and identify the responsible variables. Disease incidence is a measure of the number of new cases emerging per time unit; prevalence is the number of cases existing at any point in time in a given population. Epidemiological studies are used as a basis for public health policies and interventions (50). In the epidemiological language, the particular factors associated with disease development are often called exposure variables or risk factors, and the disease status is often called outcome or endpoint (50).

In Studies 3 and 4, the odds ratio (OR) was used to measure the associations between the exposure variables and the endpoint variables. The OR measures associations and relationships between two probabilities, the probability of an event divided by the probability of a non-event, provided that only two outcomes are possible (50). Studies 3 and 4 also use the *p*-value for hypothesis testing. The *p*-value is the probability of finding the observed difference without there being any difference between the groups, or the probability that the null hypothesis is true (50).

In Studies 3 and 4, the null hypothesis was that there were no differences between the FTD group, the AD group, and the CH group.

6.2.2 Quantitative research methods

The quantitative research methodology applies a positivist approach. Positivism is characterized by objectivity, operational definitions, replicability, and causality (132).

In quantitative studies, the investigator and the investigated subjects are independent from each other. The investigator is, therefore, able to evaluate a phenomenon without being influenced by it. The approach of quantitative research methods is characterized by orderly and disciplined procedures with tight controls (21).

The goal of quantitative research is to measure and analyze relationships between variables within a value-free framework (21). Several designs may be used in quantitative research. Studies 3 and 4 are longitudinal, case-control studies.

6.2.3 Longitudinal studies

Longitudinal studies collect data multiple times over an extended period. Such studies are useful for studying changes over time (21). Longitudinal studies are also well-suited for studying risk factors for dementia. The prodromal phase for dementia may last for several years and, therefore, it is important to determine risk factors as far ahead of disease development as possible.

In Studies 3 and 4, the potential risk factors were measured in HUNT1 (1984-86) and HUNT2 (1995-97), years before dementia diagnoses were set in the Dementia Register of Nord-Trøndelag.

6.2.4 Case-control studies

Case-control studies are observational epidemiological studies of persons with a disease of interest and a suitable control group of persons without the disease. By comparing the individuals with and without disease, the potential relationship of a suspected risk factor can be examined (50). The case-control studies are suitable for studying rare conditions and can examine a large number of possible risk factors (50).

6.2.5 Nested case-control studies

In nested case-control studies, the cases and controls are drawn from a previously examined cohort (50) (HUNT2 in Study 3 and HUNT1 in Study 4). This means that the patients, by definition, are healthy at that time. The controls are selected from patients who remain healthy at the end of the study (50).

6.2.6 Logistic regression analyses

In logistic regression analyses, the relationship between multiple independent variables and an outcome is analyzed. The probability of an event occurring is transformed into odds. For each predictor, the logistic regression yields an odds ratio (OR) (21). In Studies 3 and 4, a confidence interval (CI) of 95% was used for interval estimation. The CI is an estimate of the upper and lower confidence limits and a range of values within which a population parameter is estimated to lie at a specified probability (e.g. 95% CI) (21).

6.2.7 Ethics

Studies 3 and 4 were performed with approval from the Regional Etisk Komite (REK), the Norwegian ethics committee.

Participating patients gave written consent to take part in the HUNT1, HUNT2 (124) , and HUNT3 studies (133). They also gave written consent to allow their data from the HUNT studies to be used in studies combining HUNT data and data from hospital registers.

The retrospective part of the hospital dementia register does not have informed consent for inclusion, due to the design (134). The prospective part of the hospital dementia register used informed consent for inclusion, either from the patients or from the next of kin. The designs

of both the hospital register and the nursing home register are approved from the Regional Committee on Medical and Health Research Ethics in Mid-Norway (134).

Datasets from the Dementia Register in Nord-Trøndelag Hospital Trust and the HUNT1 and HUNT2 studies were merged using the personal identification number assigned to all the Norwegian citizens. The personal identification number was then replaced with an anonymous project identification number before the merged dataset was made available to the researchers.

7 Study 3

7.1 Aim

The aim of this study was to investigate anxiety and depression as modifiable risk factors for FTD compared with persons with AD and cognitively healthy individuals.

7.2 Method

A quantitative method using a longitudinal, case-control design was considered appropriate for this study.

7.3 Study population

The study population consisted of 84 individuals with frontotemporal dementia (FTD), 556 individuals with Alzheimer's disease (AD), and a control group of 117 verified cognitively healthy individuals (CH).

The cases of Frontotemporal dementia (FTD), Alzheimer's disease (AD), and controls of cognitively healthy individuals (CH) in our study first participated in the HUNT2 study in 1995-1997. Somewhere between 1995 and 2017, cases of FTD and AD were included in the Dementia Register after assessments for dementia diagnoses. The CH control group was selected from a follow-up project on memory and intelligence after HUNT3 between 2010 and 2011. In 2017, we performed our case-control study using a longitudinal design. All data were extracted from the HUNT2 study (Textbox 4).

Textbox 4: The Study population

1995-1997	1995-2017	2010-2011	2017
Participation In HUNT2	Included in the Dementia Register (FTD and AD groups)	Included in a follow up project (CH group)	Included in our study (FTD, AD, and CH group)

Compared to the CH group, the AD and FTD group participants were older at the time of participation in HUNT2 and were more likely to have heart disease, diabetes, metabolic disease, obesity, anxiety, and depression. Compared to the AD group, the FTD group participants were younger at the time of participation in HUNT2, as well as at the time of diagnosis. The FTD participants were also more likely to smoke, have hypertension, metabolic disease, obesity, and anxiety (Table 6). All participants in the FTD group were diagnosed with dementia after the year 2000. In the AD group, 26 participants were diagnosed with dementia between 1995 and 1999 and the remaining were diagnosed after the year 2000.

Table 2: Characteristics of the study population

	FTD	**AD**	**CH**
Number of cases in each group	**84**	**556**	**117**
Female (%)	66.7	68.7	53.0
Mean age at participation in HUNT2	67.7	71.8	61.2
Mean age at dementia diagnosis	74.4	79.2	
Risk factors present (%)			
Heart disease	15.5	16.0	6.8
Diabetes	3.6	5.0	1.7
Hypertension	32.1	29.5	29.9
Metabolic disease	11.9	8.3	6.0
Smoking	53.5	44.9	57.2
Obesity	26.2	18.0	12.8
Anxiety	29.3	21.1	8.8
Depression	13.0	13.9	2.7

7.4 Measurements

7.4.1 Anxiety and depression

In HUNT2, the Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety and depression.

HADS has 14 items that cover two subscales, one each for anxiety and depression. The HADS-A covers 7 items for anxiety, and the HADS-D covers 7 items for depression. Each item in both HADS-A and HADS-D has a four-point Likert scale (0: not present to 3: fully present). The sub-scale sum scores have a minimum of 0 and maximum of 21 (135).

The HADS-A and HADS-D sub-scale scores are categorized as 0–7: normal, 8–10: mild disorder, 11–14: moderate disorder, and 15–21 severe disorder (136).

In study 3, we included HADS scores where at least five out of the seven questions on both HADS-D and HADS-A were answered. Those who filled in five or six items were included, and their score was based on the sum of completed items multiplied with seven of five or seven of six. We used a score of 8 or above as the cut-off indicating a probable case of anxiety or depression (136).

7.4.2 Control variables

Variables that might have confounded the associations between anxiety or depression and FTD or AD were selected: sex, age at participation in HUNT2, heart disease, diabetes, metabolic disorder, hypertension, smoking, and obesity.

If the participants had positive responses to questions regarding if they had experienced angina pectoris or a heart attack, heart disease was ascertained.

If the participants had a positive response to questions regarding diabetes, diabetes was ascertained. If the participants had positive responses to questions regarding hypothyroidism or hyperthyroidism, a metabolic disorder was ascertained.

Hypertension was ascertained if participants had an average diastolic blood pressure of 90 mmHg or more.

Obesity was ascertained if participants had a BMI of 30 or higher. Smoking was categorized as never smoked on a daily basis, previous daily smoker, or daily smoker.

7.5 Statistical analysis

The association between anxiety and depression, measured by HADS in HUNT2, and the development of FTD and AD was evaluated by multivariable logistic regression. The analyses were performed using SPSS version 25.0. Ninety-five percent confidence intervals (CI) were reported and *p*-values > 0.05 were considered statistically significant.

Three analyses were performed separately: 1) analysis of person with FTD versus CH individuals; 2) analysis of persons with FTD versus persons with AD; and 3) analysis of person with AD versus CH individuals.

All three analyses were performed in four steps: 1) entering anxiety only as the variable; 2) entering depression only as the variable; 3) entering anxiety and depression as variables; and 4) entering anxiety and depression as variables and adjusting for the potential confounders of age, sex, heart disease, diabetes, hypertension, metabolic disease, smoking, and obesity.

8 Study 4

8.1 Aim

The aim of this study was to investigate smoking and obesity as modifiable risk factors for FTD compared to persons with AD and cognitively healthy individuals.

8.2 Method

A quantitative method using a longitudinal, case-control design was considered appropriate for this study.

8.3 Study population

The study population consisted of 90 individuals with FTD, 556 individuals with AD, and a control group of 117 verified cognitively healthy individuals (CH). Individuals with frontotemporal dementia (FTD), Alzheimer's disease (AD), and a control group of cognitively healthy individuals (CH) in our study first participated in the HUNT1 study in 1984-1986. Somewhere between 1995 and 2017, the cases of FTD and AD were added to the Dementia Register after assessments for dementia diagnoses. The CH control group was selected from a follow-up project on memory and intelligence after HUNT3 between 2010 and 2011. In 2017, we performed our case-control study using a longitudinal design. All data were extracted from the HUNT1 study (1984-86). (Textbox 5).

Textbox 5: The Study population

1984- 1986	1995-2017	2010-2011	2017
Participation In HUNT1	Included in the Dementia Register (FTD and AD groups)	Included in a follow up project (CH group)	Included in our study (FTD, AD, and CH groups)

The FTD and AD group participants were older at the time of participation in HUNT1 and were more likely to have heart disease and hypertension than the CH group. The participants in the FTD group had a lower mean age at the time of dementia diagnosis than the AD group. In the group of participants with FTD, 14.4% had obesity present as a risk factor, versus 14.7% in the participants with AD and 6.0% in the CH group. Of the FTD group participants, 47.8% had smoking as a risk factor, versus 39.9% in the group with AD and 46.6% in the CH group (Table 3). All participants in the FTD group were diagnosed with dementia after the year 2000. In the AD group, 26 patients received their dementia diagnosis between 1995 and 1999 and the remaining after the year 2000.

Table 3: Characteristics of the Study Population

	FTD	**AD**	**CH**
The number of participants in each group	**90**	**654**	**116**
Female (%)	70	69	52.6
Mean age at participation in HUNT1	56.6	60.7	49.1
Mean age at dementia diagnosis	74.4	79.2	
Risk factors present (%)			
Heart disease	2.2	4.1	0.9
Diabetes	1.1	0.9	1.7
Hypertension	31.1	37.3	30.2
Smoking	47.8	39.9	46.6
Obesity	14.4	14.7	6.0

8.4 Measurements

8.4.1 Smoking and obesity

In HUNT1, the participants completed self-reporting questionnaires with items on smoking status. The response options included were never smoked daily, previously a daily smoker, or current daily smoker. In study 4, previous daily smokers or current daily smokers were categorized as "smoking" and never smoked daily as "non-smoking".

In HUNT1, measurements were recorded for each participant's height and weight (height to the nearest centimeter, weight to the nearest half kilogram), and BMI was calculated and documented. We have classified patients with a BMI of 30 or higher as obese in our study.

8.4.2 Control variables

The confounders used for study 4 were sex, age at participation in HUNT1, heart disease, diabetes, and hypertension.

Heart disease was ascertained if the participants indicated that they had experienced angina pectoris or a heart attack. Similarly, diabetes was determined if responses were positive to the provided question. Hypertension was determined if participants had an average diastolic blood pressure of 90 mmHg or more.

8.5 Statistical analysis

We evaluated the association between smoking and obesity as measured in HUNT1, and development of FTD and AD using multivariable logistic regression. The analyses were performed using SPSS version 25.0. Ninety-five percent confidence intervals (CI) were reported and *p*-values > 0.05 were considered statistically significant.

Three analyses were performed independently: 1) analysis of participants with FTD versus CH individuals; 2) analysis of persons with FTD versus persons with AD; and 3) analysis of persons with AD versus CH individuals.

All of the analyses were performed in four steps: 1) smoking as the only variable; 2) obesity as the only the variable; 3) smoking and obesity as variables; and 4) smoking and obesity as variables adjusted for the potential confounders of age, sex, heart disease, diabetes, and hypertension.

9 Results

9.1 Study 1

A systematic literature search was performed in the PsychInfo, Embase, PubMed, and Cochrane databases during the period of May 2016 to April 2017.

The search resulted in 137 articles, out of which 12 articles were included. One of these studies found that diabetes increased the risk for FTD; three studies showed that head injury may increase the risk for FTD, and the prevalence of traumatic brain injury is significantly higher in patients with FTD than with other forms of dementia. One study found that autoimmune disease may be associated with increased risk of primary progressive aphasia.

The current evidence base on modifiable risk factors for FTD is too narrow to be able to draw any conclusions. Moreover, there is not enough evidence to support recommendations for lifestyle changes to prevent FTD at a population level.

9.2 Study 2

A qualitative study was carried out. Fourteen family caregivers of patients with FTD were interviewed about their experiences during the pre-diagnostic stage of FTD.

The family caregivers experienced the pre-diagnostic stage of FTD as a process of gradual changes in the interpersonal relationship with their loved one. The process was built upon following subthemes: a) becoming distant, b) becoming insecure, c) becoming devastated, and d) becoming a stranger.

The family caregivers experienced changes in their loved one for several years before the actual diagnosis. The changes were not initially interpreted as signs of disease, but eventually, these changes led to major concerns. Still, the changes were difficult to pinpoint and describe to others. The devastating and exhausting character of the process, the difficulties in describing the subtle symptoms, and a lack of awareness in clinicians may contribute to the delay in diagnosis.

The steps of the process did not necessarily have the same order for all the participants. For some participants, different steps were blended together. The family caregivers usually

experienced distance in the interpersonal relationship with the loved one early on. Additionally, a personal experience of insecurity regarding the changes was typically experienced early in disease development. Another step of the process was experiencing severe and devastating changes in their loved one. For a few participants, this step constituted the earliest step in the process.

The last step of the process for all participants was an experience of themselves and their loved one as strangers in the interpersonal relationship.

9.3 Study 3

A quantitative study with a longitudinal design was carried out. A nested case-control study was set up to assess anxiety and depression measured in the HUNT2 study as risk factors for FTD and AD diagnoses in the Dementia Register of Nord-Trøndelag.

9.3.1 Frontotemporal dementia compared to cognitively healthy individuals

In the initial analysis, with only anxiety as the variable, a significant association between anxiety and developing FTD was observed (p=0.000) (odds ratio [OR]: 4.303, 95% confidence interval [CI]: 1.925–9.622), compared with that in the CH group.

When using only depression as the variable, a significant association between depression and developing FTD was also seen (p=0.012) (OR: 5.473, 95% CI: 1.454–20.599).

When both anxiety and depression were entered as variables, a significant increase in the risk of developing FTD was observed in patients who had reported anxiety on the HADS (p=0.017) (OR: 2.947, 95% CI: 1.209–7.158). There was no significant association between depression and risk of developing FTD (p=0.151) (OR: 2.879 95% CI: 0.681–12.176). The findings regarding anxiety were consistent after adjusting for potential confounders (p=0.045) (OR: 2.797, 95% CI: 1.024–7.642).

9.3.2 Frontotemporal dementia compared to Alzheimer's disease

In the initial analysis, using only anxiety as the variable, no significant association between anxiety and developing FTD was seen (p 0.099) (OR: 1.549, 95% CI: 0.920 -2.607) when compared with observations in the AD group.

When entering only depression as the variable, no significant association between depression and developing FTD was observed (p=0.828) (OR: 0.924), 95% CI: 0.453–1.883) compared with that in the AD group.

When both anxiety and depression were entered as variables, there were no significant associations between anxiety and developing FTD (P=0.146) (OR: 1.592, 95% CI: 0.851-2.979) or between depression and developing FTD (P=0.490) (OR: 0.751, 95% CI: 0.333-1.694) compared with that in the AD group.

No significant associations for anxiety or depression were seen after adjusting for potential confounders.

9.3.3 Alzheimer's disease compared to cognitively healthy individuals

In the initial analysis, with only anxiety as the variable, a significant association with development of AD was observed (p=0.003; OR: 2.778, 95% CI: 1.404–5.498).

When using only depression as the variable, a significant association with development of AD was also seen (p=0.003; OR 5.922, 95% CI: 1.829–19.181).

When both anxiety and depression were entered as variables, a nearly significant increase in risk of developing AD was observed in patients who had reported anxiety on the HADS (p=0.054; OR: 2.009, 95% CI: 0.988–4.087). There was a significant association between depression and risk of developing AD (p=0.016; OR: 4.389 95% CI: 1.311–14.690). The nearly significant association for anxiety was reduced (p=0.114; OR: 1.967, 95% CI: 0.850–4.554) after adjusting for potential confounders. The findings regarding depression were consistent after adjusting for potential confounders (p=0.032; OR: 4.494, 95% CI: 1.139–17.731).

9.4 Study 4

A quantitative study with a longitudinal design was carried out. A nested case-control study was set up to assess smoking and obesity measured in the HUNT1 study as risk factors for FTD and AD diagnosis in the Dementia Register of Nord-Trøndelag.

9.4.1 Frontotemporal dementia compared to cognitively healthy individuals

In the initial analysis, with only smoking as the variable, no significant association between smoking and developing FTD was seen (p=0.218) (odds ratio [OR]: 0.990, 95% confidence interval [CI]: 0.975–1.006) compared with that in the CH group.

When entering only obesity as the variable, a significant association between obesity and developing FTD was observed (p=0.049) (OR: 2.629, 95% CI: 1.003–6.894).

When both smoking and obesity were entered as variables, a nearly significant increase in the risk of developing FTD was observed for obesity (p=0.064) (OR: 2.496, 95% CI: 0.947–6.582). There was no significant association between smoking and the risk of developing FTD (p=0.302) (OR: 0.992 95% CI: 0.977–1.007).

After adjusting for the potential confounders, there were no associations between smoking or obesity and developing FTD.

9.4.2 Frontotemporal dementia compared to Alzheimer's disease

In the initial analysis, with only smoking as the variable, no significant association between smoking and developing FTD was observed (p=0.600) (OR: 1.004, 95% CI: 0.990–0.017) compared with that in the AD group.

When using only obesity as the variable, no significant association between obesity and developing FTD was seen (p=0.953) (OR: 0.981), 95% CI: 0.525–1.836) compared with that in the AD group.

When both smoking and obesity were entered as variables, there were no significant associations between smoking and developing FTD (P=0.600) (OR: 1.004, 95% CI: 0.990–1.017) or between obesity and developing FTD (P=0.949) (OR: 0.980, 95% CI: 0.524–1.833) compared with that in the AD group.

No significant associations between FTD and smoking or obesity were seen after adjusting for potential confounders when compared to AD.

9.4.3 Alzheimer's disease compared to cognitively healthy individuals

In the initial analysis, with only smoking as the variable, a significant association with developing AD was seen (p=0.014; OR: 0.987, 95% CI: 0.977–0.997).

When using only obesity as the variable, a significant association with developing AD was also observed (p=0.015; OR 2.679, 95% CI: 1.211–5.928).

When both smoking and obesity were entered as variables, a significant increase in the risk of developing AD was observed both for smoking (p=0.011; OR: 0.987, 95% CI: 0.976–0.997) and obesity (p=0.013; OR: 2.736, 95% CI: 0.976–0.997) as compared with the CH group.

The significant associations disappeared after adjusting for potential confounders (smoking: p=0.0227; OR: 0.992, 95% CI: 0.979–1.005 and obesity: p=0.156; OR: 1.954, 95% CI: 0.775–4.929).

10. Methodological considerations

10.1 Combining qualitative and quantitative methods

The methods of the studies and their strengths and weaknesses are discussed separately under the sections 4.2, 5.2, and 6.2. In addition, there is a need for an overall methodological reflection on the methodological design of the thesis.

The overall aim of this thesis and the research questions required both quantitative and qualitative methods. In recent years, it has become more common to combine qualitative and quantitative methods (137). Qualitative and quantitative methods may complement each other (20). Qualitative studies are needed in order to study disease and health as dynamic processes in humans (138).

Qualitative and quantitative methods originate from different worldviews, also called paradigms. A worldview or paradigm is described as a framework of beliefs, assumptions, and philosophies that influence our experiences and interactions with the world (139). These two worldviews are often referred to as positivist (grounding quantitative methodologies) and interpretivist or constructivist (grounding qualitative methodologies) (139).

A combination of qualitative and quantitative methods and two different worldviews may pose challenges for researchers (139).

I was aware of the challenges of combining these methods. However, I strongly believed that including a qualitative study would add depth and important knowledge to the thesis. Also, I

had used qualitative methods in a former study for my master's degree. In this way, the qualitative method and phenomenological hermeneutic method were familiar to me.

One challenge of combining the two methods was to not incorporate quantification in the qualitative study. I struggled to not quantify the family caregiver's experiences of different symptoms. I needed close follow-up from my supervisors to put on phenomenological-hermeneutic glasses during my work on the analyses of the interviews. Also, it was challenging to maintain purely phenomenological hermeneutic language during the writing of the article.

Another challenge was to not treat one method as more central in the thesis. In the thesis, there is one systematic review focusing on modifiable risk factors, two case-control studies assessing modifiable risk factors, and one phenomenological hermeneutic study exploring family caregiver experiences. I have strived to focus equally on all four studies.

Qualitative and quantitative studies cannot be combined for cross validation, because they both study different phenomena (140). However, they can be complementary to each other, and we have tried to achieve that in this thesis.

10.2. Study 1

A literature review is analysis of the relevant available research literature on a topic. The purpose is to update the reader with the current literature. A good literature review should contain a clear search strategy, selection strategy, and as few personal biases as possible. In order to avoid personal bias, a systematic literature review should have an explicit and rigorous criteria to identify, evaluate in a critical manner, and synthesize the literature (141).

The systematic literature review in this dissertation followed the guidelines of the journal "Tidsskrift for Norsk Legeforening" for systematic review. The manuscript also underwent a process of review from an editor and reviewers before it was published.

I could have used a broader range of MeSH terms and keywords, for example, by including the subtypes of FTD and the diseases that overlap with FTD. This may have resulted in a larger number of articles and, perhaps, added information on modifiable risk factors regarding these diseases.

10.3 Study 2

10.3.1 Sample size

In phenomenological studies, it is common to have a small sample size, typically 10 or fewer. A sample size determination usually follows a principle of data saturation, sampling to the point that no new information is obtained, and redundancy is achieved.

In my study, I did the sampling first, which gave a sample size of 14 participants. Each participant was equally important to my study and, hence, all were included. Because of the large amount of work with the interviews, the transcription, analyses, and interpretation of the text was challenging, which may have influenced the results in the study.

10.3.1 Bias

The participants were at different stages of grief, and the interviews awoke strong feelings in several of them. This made me feel that it was my responsibility to ensure that the opinions of all participants are heard.

It was sometimes challenging to follow the semi-structured interview guide. I was affected by the participants' stories and grief. Many of the participants were very eager to tell their stories, which resulted in longer lasting interviews than planned. It would have been rude and unethical to limit their stories. This may have had an influence on the analyses, as it was challenging to handle the large amount of data.

10.3.2 Trustworthiness

In qualitative research, the concept of trustworthiness is often used instead of reliability and validity. Lincoln and Guba (1985) have outlined some standards of quality criteria for qualitative studies. They used the term "trustworthiness," which covered credibility, dependability, confirmability, transferability, and authenticity (21). Trustworthiness is the degree of confidence that researchers have in their data.

Credibility refers to the researcher's confidence in the truth value of the data and the interpretations of the data (21). Methodological validation in the study was sought by discussions with the co-authors throughout the research process, concerning study design, data collection, interpretation, and presentation of the material. Moreover, I feel that the participants in the study were appropriate to give information regarding the phenomenon of interest. The participants gave rich information with individual details. Quotes were used in the paper to show the readers some parts of the interpretation of the text.

Dependability refers to the stability or reliability of data over time (21). Would a study with the same participants and the same context give the same findings? One way to strengthen the credibility and dependability is to give participants feedback about the interpretations and obtain their reactions to it. This was not done in my study due to lack of time. Another way to strengthen dependability is to use multiple data sources: time, space, and person (21). The collection of data took about 6 months and involved interviews conducted at different times in the year, different times of a day, different places, and with participants of different ages, roles in the family, societies, and communities. The interview texts were read by all the authors, and the analyses were also conducted in cooperation with all the authors.

Confirmability refers to the researcher's objectivity (21). To achieve confirmability, the process of planning and performing the study has been documented, and codes have been used to handle the material during analyses. The paper has also been reviewed and debriefed by all authors and by a peer review journal. My preunderstanding of the phenomena was that family caregiver experiences change in their loved one several years before FTD diagnosis. Before the interviews, I expected the family caregivers to talk about symptoms and behavioral changes as the first signs of disease. Instead, they talked about the subtle changes in the relationship with their loved one. This made me believe that I succeeded in using my preunderstanding to obtain a well-designed study and still allowed myself to consider the participants' contributions to achieve different results than I expected. Hence, my preunderstanding was challenged.

Transferability is the extent to which qualitative findings can be transferred to other settings or groups. Some important aspects in transferability are data saturation, field notes, documentation of quality-enhancement efforts, and thick, vivid descriptions (21). The data material was certainly rich in information and saturated. Field notes were taken during the process of interviews and used during analyses and interpretation. The entire process of data collection, analyses, and interpretation has been described in the paper, and the findings have been discussed in relation to literature and theory.

Authenticity emerges in a report that accurately describes the events in each participant's life. The interviews were audiotaped and transcribed as soon as possible after the interview. In addition, field notes were taken. The field notes described the body language of the participants, facial expressions, tone of voice, use of humor, emotional status, and so on. This made it possible for me to use vivid descriptions and do evocative writing.

10.4 Studies 3 and 4

10.4.1 Representativeness of the HUNT population

The HUNT study probably has the most comprehensive screening data from Norway (142). The HUNT Study constitutes a population base study for health-related and medical research (130). HUNT covers the entire population within a geographical area, with a high participation rate and a wide age range and covers an extensive number of variables. The population of Nord-Trøndelag is, in many ways, representative of the population of Norway (124).

The overall participation rate was 90% for HUNT1, 70% for HUNT2, and 54% for HUNT3. In both HUNT1 and HUNT2, women were more likely to participate. The participation was highest in the 50-79 age group (124) .

Not all participants took part in all of the elements of the HUNT studies (143), potentially resulting in selection bias due to non-attendance. Some of the reasons for not attending to the HUNT1 study were that the non-attendants were busy, not interested in attending, had moved to another county, or had health problems. Of the non-attendants, 12% were less healthy or seriously ill (142).

Some of the reasons for not attending to the HUNT2 study were that the non-attendants were busy, had moved out of the county, had forgotten the invitation, or that they did not need to participate because of regular follow up by a doctor or hospital. Of these participants, 9.6% did not attend because of a disease (143).

10.4.2 Validity of dementia diagnoses

FTD and AD diagnoses from both the hospital dementia register and the nursing home register are based on clinical observations and assessments, and are validated by specialists (125).

The diagnoses of dementia in the hospital dementia register were based on clinical examinations by a physician and made according to national and international guidelines. The hospital diagnoses of AD were diagnosed according to ICD-10 criteria, and FTD was diagnosed according to Manchester-Lund criteria. Some files in the retrospective hospital data had missing files, which may have reduced the reliability of the dementia diagnoses (125).

The diagnosis of dementia in the nursing home dementia register was based on a review of data collected from patients, their family members, and their relatives. Cognitive function, dementia, neuropsychiatric symptoms, depression, quality of life, personal activities of daily life, and caregiver distress were assessed. However, a physician did not examine the patients. As for the nursing home dementia register, the nursing home diagnoses of AD were diagnosed according to ICD-10 criteria, and FTD was diagnosed according to Manchester-Lund criteria. The assessments were performed by registered nurses who conducted standardized interviews with the patients, their closest relatives, and their closest professional caregiver (125). The dementia diagnoses in the nursing home dementia register are based on symptoms presented late in the course of the disease, making it difficult to diagnose specific types of dementia, such as FTD. In the later course of AD, patients sometimes develop symptoms similar to FTD. This may have reduced the validity of some dementia diagnoses, including both FTD and AD (125).

The Dementia Register does not include patients diagnosed with dementia by the primary care system. This can be a bias, and the patients in the register may not be generalizable to the overall dementia population in Norway.

Diagnostic criteria for dementia changes over time. The data from the hospital dementia register were collected during 1995-2010. In our studies, we also have used data from the prospective part collected from 2011- 2017. The data from the nursing home register were collected during 2010-2011. This could imply that different diagnostic criteria for dementia was used.

10.4.3 Validity of anxiety and depression measured by HADS in HUNT2

In a review by Bjelland et al (2002), the validity of HADS has been studied and found to perform well in assessing the severity of symptoms and cases of anxiety and depression in the general population, as well as in psychiatry and primary care patients (135). In the review, the sensitivity and specificity of HADS-A and HADS –D with a threshold of 8+ were most often found to be in the range to 0.70 to 0.90. Previous studies have shown the HADS to be satisfactory in terms of internal consistency, factor structure, and intercorrelation (144). The self-reporting in the HADS only shows symptoms of anxiety and depression, not clinical diagnoses. Clinical diagnosis of anxiety and depression requires diagnostic work and clinical investigations from specialists.

The Norwegian version of HADS-D has recently been validated in older adults above 60 years living at home. By using ICD-10 criteria as a gold standard for a depressive diagnosis the sensitivity of HADS-D with a cutoff > 4 was 70.3% and the specificity 69.6 %. The LR+ (positive likelihood ratio) was 2.3 and LR- (negative likelihood ratio) was 0.4. The findings showed that a cutoff > 4 was best suited for identifying a depressive episode, which was in line with three other studies including older people. This may indicate underreporting of depressive symptoms in older age cohorts (145). In our studies, we used a score of 8 or above as the cutoff, indicating a probable case of anxiety or depression because this is well established for anxiety and depression in a variety of adult samples (135). The mean age of the FTD population at participation in HUNT2 was 67.7 years, the AD control group 71.8 years and in the CH control group 61.2 years. If we had used a HADS-D cutoff > 4 in our studies, we probably would have included more cases with depression. The validity of HADS should be investigated further in samples of older adults.

The observation time for HADS was symptoms of anxiety and depression experienced by the participants "last week," which could lead to recall bias in reporting as a consequence.

HADS is self-rated, and scoring could also be biased by the person's feelings at the time they filled out the questionnaire or cognitive impairment before participation in HUNT2. Understanding and interpretation of the questions in HADS may also be subject to individual variation.

10.4.4 Validity of smoking and obesity measured in HUNT1

The data on smoking were self-reported and, therefore, it is a possibility that the scoring may be biased. Differences in understanding and interpretation of the smoking items may be subject to individual variation.

The BMI of the participants in HUNT1 was calculated after measuring their height and weight (height to the nearest cm, weight to the nearest half kg). The BMI was calculated and documented. We classified obesity at BMI $\geq$30.

10.4.5 Design issues

Studies 3 and 4 are longitudinal, nested case-control studies, appropriate for assessing risk factors for dementia. The case-control studies are suitable for studying rare conditions and can examine a large number of possible risk factors (50).

The longitudinal, nested case-control design allowed us to assess anxiety and depression as risk factors for FTD 3-22 years before diagnosis in Study 3. Still, there is a possibility that the symptoms of anxiety and depression are due to the prodromal phase of FTD and AD.

The longitudinal, nested case-control design also allowed us to assess smoking and obesity as risk factors for FTD 15-31 years before the diagnosis in Study 4. However, in this study, one cannot rule out that smoking and obesity in FTD cases were due to the prodromal phase of FTD.

Both Studies 3 and 4 had two control groups, one with AD patients and one with cognitively healthy individuals. Because of the lack of studies on modifiable risk factors for FTD and the rich number of studies on modifiable risk factors for AD, it is useful to compare these two diseases. It is important to investigate similarities and differences, as these findings may aid researches in exploring new concepts in prevention and treatment.

The control group of cognitive healthy elderly individuals consisted of individuals with healthy brains. It is useful to have a control group with healthy brains, but one can argue that they may not be a true representation of the general population.

10.4.6 Sample size

While planning the study, we had a total of 100 FTD cases. We considered that this was large enough to produce a statistically significant result when adjusting for 10 covariates. However, during analyses, some cases were excluded because of missing data on variables.

In Study 3, the population of FTD patients consisted of 84 cases, while in Study 4, the population consisted of 90 cases.

Some would consider this sample size of FTD cases to be too small to give reliable or precise estimates.

A limitation of small sample size studies is that they can give a large standard error, wide 95% CI, and an imprecise estimate of effects. Another limitation is overestimation of the magnitude of an association or false negative results (47). Therefore, it is always important to interpret the results with caution (47).

However, Studies 3 and study 4 have a comparable number of FTD cases compared to other studies, where the numbers have varied from 61 to 129 cases, with the exception of-one study on head trauma as risk factor for FTD, which included 1,016 FTD cases (57).

10.4.7 Missing data

The dataset had missing data on some potential confounders for dementia, anxiety, depression, smoking, and BMI. We chose to exclude the cases with missing data, which resulted in a smaller sample size.

10.4.8 Control variables

When planning Studies 3 and 4, we wanted to include control variables that might confound the associations between anxiety/depression, smoking/obesity, and FTD/AD, like sex, heart disease, diabetes, hypertension, metabolic disease, education, brain disease, use of alcohol, smoking, and obesity.

In Study 3, we included age at participation in the HUNT2 study, gender, heart disease, diabetes, hypertension, metabolic disease, smoking, and obesity as control variables. Owing to missing data, control variables such as education, brain disease, and use of alcohol were not included.

In Study 4, we included age at participation in the HUNT1 study, gender, heart disease, diabetes, and hypertension as control variables. Owing to missing data, control variables such as education, brain disease, and use of alcohol were not included. The dataset of HUNT1 did not include metabolic or brain disease.

11. Discussion

11.1 Method and design

This thesis incorporated a systematic review of modifiable risk factors for FTD, a qualitative study on family caregivers' experiences during the pre-diagnostic stage of FTD, and two longitudinal case control studies assessing modifiable risk factors for FTD. Data from these different sources provides significant new insights into the challenges of achieving timely FTD diagnoses and possible modifiable risk factors for FTD. The major strength of this thesis is the design, in which we have combined several methods to answer the research questions. This has made it possible to achieve knowledge on both an individual and population level.

The strength of Study 1 is that no other systematic reviews have been done on modifiable risk factors for FTD. A weakness is that a broader range of MeSH terms and keywords could have been used, including the subtypes of FTD and diseases that overlap with FTD. This could

have resulted in a larger number of articles and, perhaps, added information on modifiable risk factors of these diseases.

The strength of Study 2 is that few qualitative studies exist exploring family caregivers' experiences during the pre-diagnostic stage of FTD, and the design of the study made it possible to gain a deeper understanding of this subject. The study revealed important and new findings that may be useful in development of competence regarding recognizing early signs of FTD and aid clinicians in timely FTD diagnosis. The weakness of Study 2 is that the findings cannot be generalized in a statistical way.

The strengths of Studies 3 and 4 are the longitudinal design, data of high quality on risk factors and control variables from the HUNT1 and HUNT 2 studies, and the use of both a control group with validated AD diagnoses and a validated cognitively healthy control group. To our knowledge, these are the first studies assessing modifiable risk factors for FTD in a longitudinal design with many years between exposure and outcome. The weakness of these studies is that some of the FTD diagnoses were collected from the nursing home dementia register, where the patients were not examined by a clinician and the diagnoses were set in late life and a late stage of dementia progression. Studies 3 and 4 show new and interesting findings regarding modifiable risk factors for FTD compared with control groups of AD patients and cognitively healthy individuals.

11.2 Summary of findings

The findings in Study 1 show that the current evidence base is too narrow to be able to draw any conclusions regarding modifiable risk factors for FTD. A critical evaluation of studies in this thesis included in the systematic review show that the studies use different designs, have mostly small sample sizes, lack longitudinal design, and have conflicting findings. In the systematic review, we concluded that there is not enough evidence to support recommendations for lifestyle changes in order to prevent FTD at a population level.

The findings in Study 2 shows that the family caregivers experienced the pre-diagnostic stage of FTD as a process of changes in the interpersonal relationship with their loved one. They initially interpreted these changes with natural explanations, such as a downturn period in the relationship or stress. In most of the cases, the first symptoms were subtle, but in some cases, the symptoms were more severe. Regardless of the severity of the symptoms, family caregivers found it challenging to describe and talk about this to others. The family caregivers felt rejected by the clinicians when they tried to explain their concerns, the situation, and the

changes in their loved one. In our study, we conclude that the devastating and exhausting character of the process of changes in the loved one, challenges in describing the subtle symptoms, and lack of awareness in clinicians may contribute to delay in FTD diagnosis.

Study 3 found a significant association between prior anxiety measured in the HUNT2 study (1995-1997) and FTD, and a significant association between prior depression measured in HUNT2 and AD. Additionally, a significant association was found between obesity measured in the HUNT2 study and FTD.

Study 4 found a significant association between obesity measured in the HUNT1 study (1984-1986) and FTD, and a significant association between obesity and smoking measured in HUNT1 and AD.

11.3 Comparison with other studies and interpretation of findings in the thesis

To our knowledge, no other systematic reviews on modifiable risk factors for FTD have been performed, but several studies state that modifiable risk factors for FTD are an underexplored subject (16, 52, 56, 58).

Regarding the findings in Study 2, other studies confirm that a gradual onset of symptoms is common in FTD (13, 146), family caregivers find the early symptoms of FTD subtle and difficult to recognize (13), and physicians often are unaware of neurodegenerative diseases in younger persons (84). It is well known that FTD is often misdiagnosed as depression (31, 84), midlife crises, marital conflict, stress, menopause (147), manic psychosis, obsessive-compulsive disorder, or sociopathic personality disorder (84). FTD is also considered to be underdiagnosed, because the clinical detection of FTD requires particular expertise that is possessed by few non-neurologists (148).

The findings in Study 2 suggest that the challenge of delay in an FTD diagnosis begins when family caregivers experience the first signs of changes in their love one. This is new knowledge and illuminates a less explored challenge in achieving a timely FTD diagnosis. Some of the challenges of family caregivers in recognizing the first symptoms of FTD as disease may be explained by lack of awareness of FTD in the general public. The general public is usually more familiar with Alzheimer's disease and common symptoms, such as cognitive decline (84). If the participants in Study 2 had knowledge of FTD and the early symptoms, might they have recognized the symptoms as signs as disease at an earlier stage? The problem of underdiagnosing is also a known phenomenon in early onset dementia (149).

Early onset dementia has been reported to be underdiagnosed, by as much as 30% to 50% of cases; this may be caused by a lack of knowledge of early onset dementia both in the general public and health professions (149).

Another finding was that the person with FTD often did not recognize that something had changed or something was wrong. As previously mentioned, lack of insight is known to be an early symptom of FTD. This might lead to increased insecurity in the family caregivers regarding both recognizing that something is wrong and in taking the steps into seeking help. In recent years, several studies have explored help-seeking behavior in patients (150). Delayed help-seeking is common, and delay in diagnosis and treatment are consequences of this behavior. In order to seek help, a problem has to be recognized and defined (150), obviously a challenge in FTD for both patients and family caregivers.

Underdiagnosing and misdiagnosing FTD has severe consequences in several areas. In addition to the consequences to the patients and caregivers, there are also consequences for the research field. Clinical FTD diagnoses are crucial for performing both qualitative and quantitative studies on FTD. As a result of underdiagnosis and misdiagnosis, it is challenging to determine the prevalence and incidence of FTD and obtain large FTD populations to perform studies on both modifiable and genetic risk factors. The overall consequence is a lack of support for recommendations of lifestyle changes to prevent FTD at a population level.

Interestingly, it appears that the experiences and knowledge of the family caregivers during the pre-diagnostic stage of FTD are underexplored. These experiences and knowledge may represent an unused resource that can be used to counteract delay in FTD diagnosis. Increased public knowledge about FTD could lead to earlier help-seeking in family caregivers of persons with FTD. Moreover, increased knowledge regarding FTD among clinicians could lead increased attention to family caregivers' stories and prevent rejections. Bang et al (2015) state that the preclinical phenomenology of FTD needs to be better characterized, and further development of molecular biomarkers and neuroimaging may lead to earlier detection and potentially prevent or reverse the pathological process (151). These tools are not yet available, but the family caregivers' experiences are available. According to Bang et al (2015), the current routine behavioral and emotional assessments used in the diagnostic work of FTD are not sensitive enough to predict disease onset (151). It is likely, that the experiences of family caregivers may aid clinicians in developing new diagnostic assessments regarding the early signs of FTD.

To perform studies on modifiable risk factors for FTD, one must have an available population of individuals with validated FTD diagnoses. The Dementia Register in Nord-Trøndelag Health Trust made this possible for Studies 3 and 4. Additionally, we had the ability to achieve a longitudinal design using the HUNT1 and HUNT2 studies.

To our knowledge, no other studies have assessed anxiety and depression as risk factors for FTD, but other studies have found associations between anxiety and AD or dementia in general (95-101). A few hypotheses have suggested how anxiety might be damaging to the brain. The main brain region involved in fear is the amygdala (152). The amygdala receives sensory information from thalamus and then initiates responses in the behavioral and automatic nervous systems. Threat responses are suggested to be modulated by the prefrontal regions in the brain and the hippocampus (152).

Clinical anxiety neurochemistry is complex. In relation to dementia in particular, the hypothalamic-pituitary-adrenal (HPA) axis is mentioned (101). This is a system of hormones released in response to anxiety, including glucocorticoids and cortisol (152). A recent review examining the relationships between cortisol, cognitive impairment, and AD, found that elevated cortisol was associated with decreased cognitive function and a higher risk of AD (153). High levels of cortisol have been linked to decreased brain volume, particularly the occipital and frontal gray matter volumes, as well as the hippocampus (153).

Another recent review found anxiety as a risk factor for both AD and vascular dementia (104). The authors suggested that neurotoxic distress characterized by anxiety may lead to alterations in glucocorticoids that may affect the neurons. In addition, anxiety may lead to avoidance behavior and an inactive lifestyle, both known to be risk factors for dementia (104).

A mediating factor in this area could be anxiety treatment by benzodiazepines. Some studies have found benzodiazepines to be a risk factor for AD (103).

A review from 2016 found a possible correlation between prolonged stress and anxiety with structural degeneration of the hippocampus and impaired function in the prefrontal cortex (154). Another hypothesis of the associations between anxiety and dementia is that apolipoprotein E (APO E) may be linked to anxiety as well as dementia (102). APO E is the most important genetic risk factor for AD (155). However, the association between APO E and FTD is not clear. Some studies have found associations between APO E and FTD, others

have not found such associations. Several of these studies have been based on small samples (155).

No other studies have assessed depression as risk factor for FTD, but depression has been found to be a risk factor for dementia in several studies (39, 107-111). Depression is also suggested to be damaging to the brain. Similar to anxiety, depression may lead to increased glucocorticoid production and, possibly, atrophy of the hippocampus. In fact, reduced hippocampus volume has also been found in individuals with depression (112). Some studies have shown that AD patients with depression have a larger number of plaques in the hippocampus compared to AD patients without depression. It has also been suggested that the increased number of plaques are due to a stress response associated with depression and glucocorticoids (112).

Depression is also related to lifestyle habits such as smoking and inactivity that again may lead to obesity and metabolic syndrome. These are all known risk factors for dementia. Depression also increases the risk for myocardial infarction and stroke, also risk factors for dementia (112). In addition, a few studies suggest that chronic inflammation is a link between depression and dementia. Increased cytokine levels found in patients with depression may indirectly lead to increased pro-inflammatory changes in the central nervous system (CNS) and dementia. Pro-inflammatory cytokines also interfere with serotonin metabolism (112). Brain-derived neurotrophic factor is necessary for neuronal health, and its deterioration has been detected in both individuals with depression and AD (112).

Some of the earliest symptoms of FTD are known to be similar to symptoms of psychiatric disorders (45). Assessment of anxiety and depression by HADS in the HUNT2 study was performed during 1995 to 1997. All the cases of FTD received their FTD diagnoses in 2000-2017. This gives a range of 5-22 years between the assessment of anxiety or depression and an FTD diagnosis. Little is known about the length of prodromal phase in FTD (48), but studies have found it can take from 5 to 10 years to obtain an accurate correct diagnosis (9, 49). Therefore, we cannot rule out that the anxiety noted in FTD patients is a part of prodromal phase of FTD. The measurements in HADS do not indicate the duration of anxiety symptoms. As for the FTD cases, we cannot rule out the possibility of the symptoms of depression being a part of the prodromal phase of AD. AD is known to develop slowly over 1 to 10 years or longer (156).

To our knowledge, only two other studies have assessed smoking as a risk factor for FTD. A recent study by Tremolizzo et al (2017) assessed tobacco consumption in FTD outpatients and controls and found no association between FTD and smoking (157). This in line of the findings in our study. Smoking has also been included as a control variable in some studies on risk factors for FTD. In these studies, no significant associations between smoking and FTD has been found (16, 54, 55). However, the study by Atkins et al (2012) found significant associations between smoking and FTD (53). A potential explanation for these contradictory findings between this study and Study 4 may be differences in the mean age of onset of dementia and differences in dichotomizing the smoking variables in the two studies.

Smoking is a well-known risk factor for dementia in general (39, 118) and AD (28, 39). Mechanisms proposed for the association between smoking and dementia are cerebrovascular disease, stroke, heart disease, increased total plasma homocysteine, atherosclerosis, and oxidative stress (118). Increased plasma homocysteine is associated with atherosclerosis, cardiovascular disease, and stroke (119). In addition, smoke contains several toxic chemicals, which are known to damage brain cells and, in turn, increase the risk of stroke (120).

Obesity has been even less frequently assessed as a risk factor for FTD. The study by Atkins et al (2012) found significant associations between smoking, obesity, and FTD (53). This is in line with the findings in Study 4. Only one other study has used obesity as a control variable, in which no significant associations were found (52).

Several studies have found obesity to be a risk factor for dementia in general (39, 41, 121). Mechanisms that have been proposed for the association between obesity and dementia are diabetes, cardiovascular disease, hypertension, increased inflammation, and higher levels of cytokines (121). Obesity has been associated with decreased brain volume, and grey matter atrophy in the temporal, frontal, and occipital cortices, hippocampus, thalamus, and midbrain (122). Obesity has also been associated with decreased blood flow in the prefrontal cortex of the brain and an increase in brain age (122). Obesity is associated with decreased brain volume, and grey matter atrophy in the temporal, frontal, and occipital cortices, hippocampus, thalamus, and midbrain (122).

Interestingly, significant associations between obesity and FTD were found in both Study 3 and Study 4. The cases and controls in Studies 3 and 4 had participated in both the HUNT1 study and the HUNT2 study and smoking and obesity were assessed in both of our studies.

In 1984-1986 (Study 4), the mean age at participation in the HUNT1 study was 56.6 years in the FTD group, 60.7 years in the AD group, and 49.1 years in the CH group. When comparing the FTD group with the CH group, the unadjusted analyses showed significant associations between FTD and obesity. When comparing the AD group with the CH group, the unadjusted analyses showed significant associations between both smoking and obesity and AD.

In 1995-1997 (Study 3), the mean age at participation in the HUNT2 study was 67.7 in the FTD group, 71.8 in the AD group, and 61.2 in the CH group. In the adjusted analyses, a significant association between FTD and obesity was seen, when comparing with CH individuals. However, the significant association between AD and both smoking and obesity seen in Study 4 was not present in Study 3.

Obesity appears to be a risk factor that would be interesting to explore further in relation to FTD in future longitudinal studies. Perhaps obesity at midlife and onward may be a risk factor for FTD. Many of the FTD cases in the material consist of cases diagnosed in the nursing home register. These cases were diagnosed during 2010-2011, presumably after several years living with dementia. Perhaps these cases had developed poor dietary habits as a result of prodromal phases already in 1984-1986. If so, this adds new and important findings regarding the prodromal phase of FTD. Another possibility is that anxiety may lead to avoidance behavior and inactive lifestyle, which again may lead to obesity. Perhaps this anxiety was present already in 1984-1986.

When it comes to the AD group, the findings from both studies suggests that there are significant associations between AD and smoking and AD and obesity in 1984-1986, but not in 1995-1997. However, in 1995-1997 the variables of smoking and obesity were used as control variables and not exposure variables, which may have an impact on the findings. The findings might have been different if smoking and obesity were used as exposure variables. A significant association could have been observed before adding control variables into the analyses. Could obesity and smoking at an earlier age be a risk factor for AD, but not smoking and obesity in advanced age? This is not supported by other studies. For instance, Povova et al (2015) found in their review that obesity in both middle age persons and the elderly was associated with increased risk for AD (41).

In both studies, when comparing FTD to AD, no significant associations were found in either the exposure variables or confounding variables. An explanation might be that the FTD group was significantly smaller than the AD group, or that some of the cases in the FTD group

might have AD and not FTD. Assessment of smoking and obesity in HUNT1 study was performed during 1984 to 1986. All the cases of FTD received their FTD diagnoses in 2000-2017. This gives a range of 15 to 31 years between the assessment of smoking and obesity and an FTD diagnosis. Even if little is known about the length of the prodromal phase of FTD, we find it unlikely that the obesity is related to the prodromal phase of FTD. However, we cannot rule out the possibility.

Clearly, anxiety, depression, smoking, and obesity might be damaging to the brain both through neuroanatomical and neurochemical processes and might also result in lifestyle variables that are risk factors for dementia. Could anxiety particularly be damaging to the frontal lobe of the brain, while depression is more damaging to the hippocampus in the brain? A full understanding of the neuroanatomical and neurochemical processes of anxiety, depression, obesity, and smoking is complex and requires special expertise. However, our findings suggest that obesity might be a risk factor for FTD from midlife onwards and that anxiety is a risk factor for FTD. Our findings also suggest that depression, smoking, and obesity are risk factors for AD.

11.4 Conclusion

Our studies have shown that it is possible to perform both qualitative and quantitative studies to fill in the lack of knowledge contributing to delays in FTD diagnoses and lack of modifiable risk factors for FTD. The knowledge on early signs of disease and development of FTD is to be found in the family caregivers. Exploring this knowledge may aid in timely diagnosis of FTD. Detection, diagnosis, and registration of FTD diagnoses gives a foundation for research on both genetic and modifiable risk factors for FTD. Detecting modifiable risk factors of FTD may result in prevention of FTD and a better understanding of the pathology of FTD.

WHO lists several risk factors for dementia in general (2). In AD, several modifiable risk factors have been detected, making it possible for the government to propose guidelines for the diagnosis and prevention of Alzheimer's disease (113). Unfortunately, this is not yet possible for FTD. In the WHO global action plan on the public health response to dementia, there is a vision of preventing dementia and a supporting a meaningful life with dignity for people with dementia and their caregivers (2). To achieve appropriate support and treatment, it is important to obtain a correct dementia diagnosis. The Norwegian Ministry of Health and

Care Services has a goal to create a more dementia-friendly society based on openness, understanding, and respect by implementing the "Dementia Plan 2020". The plan has been developed in close cooperation with people who have dementia and their family caregivers. Some of the strategies include timely diagnosis, close post-diagnostic follow up, research, knowledge, and competence (158).

The "Dementia Plan 2020" does not mention FTD specifically, but states that there is still a considerable lack of expertise in both specialists and primary health services regarding diagnosing dementia (158). We argue that this lack of expertise particularly concerns FTD.

Building knowledge about FTD in the general public specialists, and primary health services is time consuming, but a good starting point is clinicians paying attention when family caregivers show concern about personality and behavioral changes or loss of functions in a loved one. Moreover, it is important to remember that persons suffering from FTD often have a lack of insight and, therefore, are unable to participate in developing strategies (84) such as the "Dementia Plan 2020". The family caregivers, however, have the ability to advocate on their behalf (84).

12 Clinical implications

Study 1 has provided health professionals with an up-to-date review of modifiable risk factors for frontotemporal dementia. The findings in Study 1 show that the current evidence is not enough to recommend lifestyle changes to prevent frontotemporal dementia. Family caregivers are often curious when it comes to explanations of disease or risk factors for disease. In addition, they worry about the risk of developing FTD themselves, either through genetics or lifestyle habits. Clinicians can use the findings in Study 1 to give family caregivers an overview of the modifiable risk factors that have been investigated for frontotemporal dementia. In addition, clinicians can use the findings in this study to inform the family caregivers that it is still not possible to recommend lifestyle changes to prevent FTD.

Study 2 has provided knowledge about family caregivers' experiences during the pre-diagnostic stage of FTD. The knowledge from Study 2 can aid general practitioners, psychiatric units, and geriatric units in recognizing the symptoms of FTD, earlier FTD diagnostic assessments, and earlier establishment of support for patients and family

caregivers. Study 2 may teach health professionals that lack of insight might be an early symptom of FTD, and the family caregiver might struggle to persuade their loved one to meet a clinician. Moreover, Study 2 may educate health professionals to show patience, empathy, and appreciate family caregivers as important informants; their observations must be considered.

Study 3 and 4 are epidemiological studies and, therefore, they do not provide specific clinical implications. However, anxiety and depression disorders are common in the general population. Studies show that anxiety and depression might be risk factors for dementia in general, but also could be prodromal signs of dementia. Health professionals should aim to provide treatment and follow up in patients with anxiety and depression. Moreover, they should be aware that anxiety and depression might be the first signs of dementia in both FTD and AD.

Smoking and obesity are two of the five leading global risk factors for mortality (113). Smoking increases the risk of cancer, heart disease, stroke, chronic respiratory disease, and dementia (114). Obesity is increasing worldwide due to a decrease in physical activity and dietary changes. Several studies have observed obesity and smoking as risk factors for dementia (3, 41-43, 95, 115-117). Health professionals should aim to give patients support and advice when it comes to diet, physical activity, and smoking, due to the significant implications these factors have on health in general. In addition, health professionals should be aware that binge eating, changes in dietary habits, and an increase in smoking may be symptoms of FTD.

13 Further research

In the future, more studies assessing the modifiable risk factors for FTD should be carried out, followed by reviews of modifiable risk factors of FTD. This would help clinicians to have increased knowledge regarding modifiable risk factors for FTD and to give recommendations about changes in lifestyle habits to prevent FTD.

Future research on early or pre-diagnostic stage FTD should aim to include family caregivers of persons suffering from FTD. The knowledge of family caregivers may inspire researchers or clinicians to develop an interview assessment of early symptoms based on emphatic listening. This would be useful for clinicians when family caregivers struggle to explain the early signs of the disease. Additionally, the experiences of family caregivers should be

included in further research to develop better support for both patients and family caregivers at the early stage of disease and onwards.

To study modifiable risk factors for FTD, large populations with confirmed FTD diagnoses must be sampled for research studies. Hospitals and hospital units should cooperate to establish FTD registers. Future research on modifiable risk factors for FTD should use longitudinal designs with long follow up periods to avoid bias in the prodromal phase.

Future research on modifiable risk factors for FTD should also analyze genetic data to separate genetic and sporadic cases of FTD. This will provide further knowledge of the possible relationships between modifiable and non-modifiable risk factors for FTD.

Further research on modifiable risk factors for FTD should aim to compare FTD with both cognitively healthy individuals and AD.

14 Overall Conclusions

This thesis has contributed new knowledge about the earliest symptoms of FTD by illuminating the experiences of family caregivers during early stage FTD. Study 2 shows that education of general public and health professionals about FTD is an important step in achieving earlier FTD diagnoses.

This thesis has contributed to new knowledge of modifiable risk factors for FTD by providing an up-to-date review of modifiable risk factors for FTD and investigating anxiety, depression, smoking, and obesity as modifiable risk factors for FTD.

Our studies on modifiable risk factors for FTD have used data and designs of good quality. However, the results must be interpreted carefully. The contribution of knowledge regarding modifiable risk factors of FTD from our studies is only a tiny piece of the puzzle. The research field of modifiable risk factors for FTD is still considered sparse and, therefore, more studies need to be performed in the future to draw conclusion. We hope that the data from our study will be useful in designing larger confirmatory studies.

15. References

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Original Publications (paper 1-4)

Appendix 1- Informant letter to the participants in Study 2
Appendix 2- Interview guide used in Study 2
Appendix 3- Questionnaires in HUNT1
Appendix 4- Questionnaires in HUNT2

Paper 1

Tidsskriftet
DEN NORSKE LEGEFORENING

Risk factors for frontotemporal dementia

OVERSIKTSARTIKKEL

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BACKGROUND

Risk factors for frontotemporal dementia are poorly understood. The purpose of this article is to provide an up-to-date review of modifiable risk factors for frontotemporal dementia and to evaluate the evidence base for clinical recommendations on how to reduce risk.

METHOD

Searches were performed in the PsychInfo, Embase, PubMed and Cochrane databases in the period May 2016 to April 2017. The search yielded 137 articles, of which 101 were excluded because they concerned only genetic aspects of frontotemporal dementia and non-modifiable risk factors. After reading 36 articles in full, we selected 12 articles that were either reviews or original studies.

RESULTS

Some studies showed an association between modifiable risk factors and the development of frontotemporal dementia. One study found that diabetes gives rise to increased risk. Three studies showed that head injury can increase the risk of frontotemporal dementia and that the prevalence of traumatic brain injury is significantly higher in patients with frontotemporal dementia than with other forms of dementia. Autoimmune disease may be associated with increased risk of primary progressive aphasia, a subtype of frontotemporal dementia.

INTERPRETATION

The literature suggested an association between diabetes, head injury, autoimmune disease and frontotemporal dementia. There is currently insufficient evidence on which to base recommendations for lifestyle changes to prevent frontotemporal dementia at the population level.

The umbrella term *frontotemporal dementia* encompasses several neurodegenerative diseases that lead to neuronal loss in the frontal and/or temporal lobes (1). Frontotemporal dementia can be divided into two phenotypic groups on the basis of changes in either behaviour or language. The behavioural variant accounts for about half of all cases and includes changes in behaviour and personality (2). This variant is characterised by focal and prominent frontal atrophy. The language variant is called primary progressive aphasia and consists of three subtypes: a non-fluent variant (known as progressive non-fluent aphasia), a semantic variant (known as semantic dementia) and a logopenic variant (known as logopenic aphasia) (3–5). The semantic variant is characterised by bilateral anterior temporal lobe atrophy and is associated with language difficulties, compulsions and impaired emotional processing (3). Frontotemporal dementia overlaps with other neurodegenerative diseases such as progressive supranuclear palsy, corticobasal degeneration and behavioural variant frontotemporal dementia with motor neuron disease (6) (Box 1).

Box 1 Frontotemporal dementia

Term encompasses the following disorders (3–6):

1. Behavioural variant. Accounts for about half of all frontotemporal dementia cases and includes altered behaviour and personality
2. Language variant (primary progressive aphasia). Consists of three subtypes:
    - Non-fluent variant (progressive non-fluent aphasia)
    - semantic variant (semantic dementia)
    - logopenic variant (logopenic aphasia)

Frontotemporal dementia also overlaps with other neurodegenerative diseases:

- Progressive supranuclear palsy
- Corticobasal degeneration
- Behavioural variant of frontotemporal dementia with motor neuron disease

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Many patients with frontotemporal dementia show symptom onset in their fifties or sixties, with some individuals affected as early as their thirties or forties (7). The interval between symptom onset and diagnosis may be up to five years (8, 9), and there is currently no curative treatment (10). Risk factors for dementia can be divided into modifiable and non-modifiable (11). Knowledge of modifiable risk factors is important for clinicians who wish to offer patients advice on how to prevent or reduce the risk of developing dementia.

Frontotemporal dementia is one of the most common forms of dementia in those under the age of 65 (4), and is thought to account for about 10 % of all cases in this age group (12). The prevalence of dementia under the age of 65 in Norway has been estimated at 1 200–1 400 cases, but up-to-date figures are not available for incidence and prevalence among younger persons (8). A family history is one of the major risk factors for frontotemporal dementia, but up to 60 % of those affected have no known family members with the condition (13). This indicates that 6 out of 10 cases are sporadic (non-hereditary) (13). Frontotemporal dementia is linked to chromosome 17 in some families, with an autosomal dominant inheritance pattern, and to chromosomes 3 and 9 in other cases. Mutations in the tau gene have also been detected in certain cases (14). Knowledge of modifiable risk factors for frontotemporal dementia can therefore play a key role in understanding who is affected.

The purpose of this article is to provide an up-to-date review of modifiable risk factors for frontotemporal dementia and to evaluate whether the evidence base is sufficient to provide clinical recommendations aimed at reducing risk.

Method

We conducted a systematic search in the PsychInfo, Embase, PubMed and Cochrane databases, using the MeSH terms and keywords 'frontotemporal degeneration', 'frontotemporal dementia', 'frontotemporal lobar degeneration', 'dementia', and 'risk factors'. The search was limited to articles published in the period 1 January 2005 to 24 January 2017. The search was filtered by the following languages: Norwegian, Danish, Swedish and English.

The inclusion criteria were that articles should be reviews or original studies with data on modifiable risk factors for frontotemporal dementia. Studies of non-modifiable risk factors as well as all case reports, opinion pieces and conference proceedings were excluded. The search yielded 137 articles, of which 101 were excluded because the title revealed that they were not about modifiable risk factors. A total of 36 articles were read in full, of which a further 25 were excluded because they did not relate to modifiable risk factors. The 11 articles included were all either review articles or original studies with data on modifiable risk factors for frontotemporal dementia. An article from the reference list of one of the 11 was included in addition, bringing the total to 12 articles (Figure 1, Table 1) (13, 15–22).

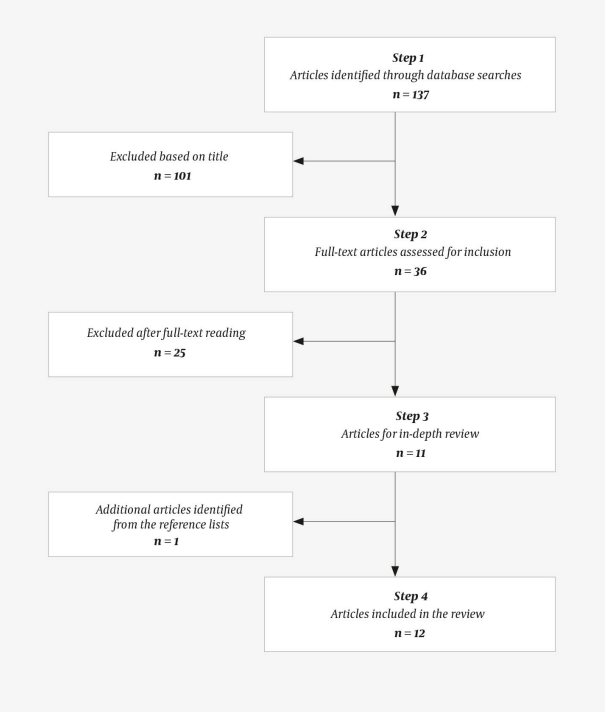

Figure 1 *Flow chart for the literature search*

Table 1

Risk factors for frontotemporal dementia (FTD) in the studies selected

Study	Country	Setting	Sample	Main finding
De Reuck, 2012 (15)	France	A memory clinic and a hospital	22 brains from deceased persons diagnosed with FTD *Control group:* 15 brains from deceased persons with no history of brain disease	Cerebrovascular risk factors and lesions were less common among persons with FTD, whereas changes in white matter were more prevalent and more severe
Golimstok, 2014 (16)	Argentina	Hospital	100 persons with FTD *Control group* 200 persons without dementia or any other neurological disease	Diabetes was identified as a risk factor for FTD.
Kalkonde, 2012 (17)	USA	Memory clinic	63 patients with behavioural variant FTD *Control group:* 491 patients with another form of dementia	Patients with FTD had a higher prevalence of traumatic brain injury and lower prevalence of cardiovascular disease and cerebrovascular disease than the control group.
Torralva, 2015 (18)	USA	Hospital	62 patients with behavioural variant FTD and cerebrovascular disease *Control group:* 329 patients with behavioural variant FTD without cerebrovascular disease	The FTD group was older at disease onset and had more cases of stroke and hypertension than the control group.

Study	Country	Setting	Sample	Main finding
Borroni, 2008 (19)	Italy	Hospital	117 patients with FTD *Control groups:* 400 patients with Alzheimer´s disease 55 patients with progressive supranuclear palsy 55 patients with corticobasal degeneration	The FTD patients: • were younger than the control groups with Alzheimer's disease and progressive supranuclear palsy. • had a stronger family history of dementia than the patients with Alzheimer's disease. • had a higher prevalence of *APOE*-risk genotype than the control groups with corticobasal degeneration and progressive supranuclear palsy. • had a higher educational level than the control group with Alzheimer's disease. • had a lower prevalence of cardiomyopathy and hypertension than the control group with Alzheimer's disease. • had a lower prevalence of hypertension than the control group with progressive supranuclear palsy.
Rosso, 2003 (13)	Netherlands	Hospital	80 patients with sporadic FTD *Control group:* 124 patients without cognitive impairment or dementia	The FTD patients had a higher prevalence of head injury and metabolic disease than the control group.
Miller, 2013 (20)	USA	Academic medical centre	129 patients with the semantic variant of primary progressive aphasia *Control groups:* 39 patients who were progranulin mutation carriers 186 patients with normal cognition 158 patients with Alzheimer's disease	The FTD patients and the control group of progranulin mutation carriers had an increased prevalence of certain autoimmune diseases compared to the control groups with normal cognition or Alzheimer's disease.
Deutsch, 2015 (21)	USA	Academic medical centre	1 016 patients with FTD *Control group:* 2 015 patients without cognitive impairments	Head injury with loss of consciousness was more common in patients with FTD than in the control group.

Study	Country	Setting	Sample	Main finding
Atkins, (2012) (22)	Australia	Research centre	62 persons with early Alzheimer's disease *Control group:* 61 persons with early FTD	There were more smokers and individuals with higher body weight among patients with FTD than in the control group with early Alzheimer's disease.

The literature review was performed in accordance with the PRISMA criteria (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (23).

EDUCATION

A high educational level is considered to be protective against Alzheimer's disease and vascular dementia (19). The relationship between educational level and frontotemporal dementia, progressive supranuclear palsy and corticobasal degeneration has also been examined (19). The analysis included risk factors such as family history, cardiomyopathy, hypertension, hypercholesterolaemia, diabetes and apolipoprotein genotype, and was adjusted for age and gender. The analysis compared 117 patients with frontotemporal dementia with control groups comprising 400 patients with Alzheimer's disease, 55 with primary supranuclear palsy and 55 with corticobasal degeneration. The results revealed that persons with frontotemporal dementia were on average younger at disease onset, had higher levels of education and were more likely to have family members with dementia than the control groups (19).

CARDIOVASCULAR RISK FACTORS

Another study from 2014 found that approximately 60 % of patients with frontotemporal dementia were sporadic cases (16). The study included 100 patients with frontotemporal dementia and a control group of 200 persons. After adjusting for gender, age, diabetes, hypertension, overweight, dyslipidaemia, hypothyroidism and osteoporosis, a significant association was found between frontotemporal dementia and type 2 diabetes compared with the control group. Type 2 diabetes was shown to be an independent risk factor for frontotemporal dementia (16).

In 2015, researchers found that it was more difficult to diagnose frontotemporal dementia in persons who had previously had a stroke (18). Patients with the behavioural variant of frontotemporal dementia more often had hypertension and a history of stroke. The findings of this study suggest that cerebrovascular disease should not be ruled out in cases of behavioural variant frontotemporal dementia (18).

Another prospective study found that persons with early Alzheimer's disease had an almost three times greater risk of hypertension than those with early frontotemporal dementia, whereas smoking and overweight were more common in the group with early frontotemporal dementia (22). With the aid of 22 brain biopsies, researchers found that cerebrovascular lesions were less common in persons with frontotemporal dementia compared with healthy control subjects, but that white matter changes occurred more often. These should therefore not be used in isolation as a prognostic indicator (15).

HEAD INJURY

Head injury was associated with an increased risk of frontotemporal dementia, with an odds ratio of 3.3 in a cohort of 80 patients with sporadic frontotemporal dementia versus a control group of 124 persons without cognitive impairment (13).

In another study, a cohort of 63 patients with behavioural variant frontotemporal dementia was compared to a control group of 491 patients with another form of dementia. Traumatic brain injury was found to be more common in the patients with frontotemporal dementia (17).

A major study that included 1 016 persons with frontotemporal dementia and a control group of 2 015 persons without cognitive impairment showed that head injury with loss of consciousness was more common in patients with frontotemporal dementia and may increase the risk of the disorder (21).

AUTOIMMUNE DISEASE

One study has shown an increased prevalence of specific autoimmune diseases in patients with the semantic variant of primary progressive aphasia and in progranulin mutation carriers compared to healthy control subjects and control subjects with Alzheimer's disease (20).

Discussion

Our literature review demonstrates that few studies have examined modifiable risk factors for frontotemporal dementia (4, 5). It is important to note that early symptoms of frontotemporal dementia may include impulsive and disinhibited behaviour leading to, for example, hyperorality, with increased consumption of carbohydrate-rich foods in particular, or increased use of alcohol and tobacco (1, 3). Little is known about the length of the prodromal phase in frontotemporal dementia, but studies show that it may take up to five years from the initial examination for a diagnosis to be made (8).

The study showing that patients with frontotemporal dementia are younger and have higher educational levels than patients with Alzheimer's disease, used persons with other dementia disorders as controls. This may result in selection bias owing to differences in age of onset between the disorders (19). Another source of bias must also be considered: Higher education is more common among younger persons than among older generations, and frontotemporal dementia often affects younger individuals.

In terms of cardiovascular risk factors, a significant association was found between frontotemporal dementia and type 2 diabetes in one study (16), and between smoking, overweight and frontotemporal dementia in another (22). In case-control studies, overweight and smoking may be viewed as modifiable risk factors for frontotemporal dementia, but they may also form part of the prodromal phase.

There are conflicting findings in two studies regarding the status of hypertension as a risk factor: Kalkonde *et al.* found a fairly similar prevalence of hypertension in patients with frontotemporal dementia versus other forms of dementia (17), whereas Atkins *et al.*, who included a cohort of individuals with early-stage frontotemporal dementia and a control group with early-stage Alzheimer's disease, found hypertension to be more common in Alzheimer's disease (22). One reason for the divergent findings may be that one of the studies used a younger disease cohort and a younger control group.

Three studies show that head injury increases the risk of developing frontotemporal dementia. One of these studies featured a markedly larger disease cohort than all of the other studies we identified, with 1 016 persons with frontotemporal dementia (21). Head injury is thus the most studied risk factor, but two of the studies have small sample sizes and all three use different definitions of head injury. One study found an association between autoimmune disease and the semantic variant of primary progressive aphasia (20). This study includes no control variables in terms of other diseases or lifestyle variables, which should be considered a weakness. It is unclear whether there is an association between systemic autoimmune disease and frontotemporal dementia.

Conclusion

The literature suggests associations between diabetes, head injury and autoimmune disease, and frontotemporal dementia, but the current evidence base is too narrow to be able to draw any conclusions. There is insufficient evidence to support recommendations

for specific lifestyle changes aimed at preventing frontotemporal dementia at the population level.

MAIN MESSAGE

We found no studies that were able to show an effect of treatment in slowing or preventing the development of frontotemporal dementia

Head injury was the biggest risk factor for frontotemporal dementia among those examined in this study

Given that no treatment currently exists, there is a major need for more research on how to prevent frontotemporal dementia

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Family caregivers experiences of the pre-diagnostic stage in frontotemporal dementia

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ABSTRACT

Frontotemporal dementia (FTD) is a neurodegenerative disease with symptoms that differs from other dementias. Commonly early symptoms in FTD are changes in personality and behavior, which can be interpreted as psychiatric disease. The delay in FTD diagnosis contributes to the burden of family caregivers. Therefore, it is important to have more knowledge about the pre-diagnostic stage. In this qualitative interview study, we explored fourteen family caregiver's experiences of the pre-diagnostic stage of frontotemporal dementia (FTD). Our findings suggest that the family caregivers experienced the pre-diagnostic stage of FTD as changes in the interpersonal relationship with their loved one. These changes were often subtle and difficult for family caregivers to explain to others. The findings from our study illuminate the importance of medical staff paying attention when a next of kin is concerned about subtle changes in a loved one. The findings also illuminate that awareness of FTD should be raised.

Introduction

Dementia is an umbrella term for several diseases causing damaging, degenerative changes in the brain. The most common types of dementia are Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (FTD).[1] Studies show that family caregivers experience the early stage of dementia as a complex phase of sense making and recognizing of early symptoms.[2]

Frontotemporal dementia (FTD) is a neurodegenerative disease that affects the frontal or temporal lobes in the brain, or both. These areas in the brain have important functions when it comes to behavior, planning, problem-solving, emotional control, and speech.[3] FTD encompasses three clinical variants: a behavioral variant (bv-FTD) and two language variants: semantic dementia and progressive no fluent aphasia.[4, 5]

FTD accounts for 10% of all confirmed dementias in individuals with onset before 65 years.[6, 7] It is most often diagnosed between the ages of 45 and 65, but it can also affect younger and older people.[3] The average age of diagnosis is 57 years old.[8] FTD is progressive and leads to death, on average about 80 months after caregivers notice the first symptoms.[9] There exists no cure for FTD today.[10] The only treatment available is selective serotonin reuptake inhibitors (SSRIs) to relieve symptoms.[7] Support for patients, families and caregivers is the most important interventions.[10]

The symptoms of FTD include personality changes, behavioral changes, and sometimes language deficits.[11] The symptoms are often accompanied by psychiatric symptoms, such as obsessions, mania, depression, compulsions and psychosis.[12] These symptoms are different from the memory deficits associated with more common types of dementia.[3, 13] In addition, a gradual onset is one of the hallmarks of FTD[14, 15] and the early symptoms are subtle and difficult to recognize for family caregivers.[15] The symptoms often are interpreted by the family caregivers as variations in mood and personality,[15] fatigue, stress, overwork, or depression.[16] In addition, sometimes one of the first symptoms in FTD is lack of insight.[15] An early frontotemporal diagnosis is important to achieve, but this often takes up to 5 years.[7] The symptoms are often interpreted as neurological or psychiatric disorders by clinicians.[17,7]

Studies show that being a family caregiver to a person with FTD is particularly challenging and burdening[13] because of the behavioral and personality changes, often young onset, and the delay in diagnosis.[12, 18–21] Misdiagnosis or delay in correct diagnosis reduces the family caregivers' possibilities to seek supportive resources, support, and management.[17]

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FTD presents a diversity of symptoms and recognition and awareness of the earliest symptoms may contribute to earlier FTD diagnosis.[12] To our knowledge, no other qualitative studies have investigated the experiences of family caregivers of the pre-diagnostic stage of FTD. The knowledge of family caregiver's experiences would contribute to increased public, medical and nursing knowledge of FTD as well as its pre-diagnostic stage and symptoms. This may benefit to in earlier correct FTD diagnosis. The aim of our study was therefore to explore the family caregivers' experiences of the pre-diagnostic stage of FTD.

Materials and methods

Design

In order to achieve a deep understanding of how the family caregivers experienced their lives with their loved ones, we conducted a qualitative study in the Gadamerian hermeneutic tradition. Gadamer (1990) used the question "How is understanding possible?" to outline his philosophical hermeneutic theory. According to Gadamer (1993), all humans are part of history, and it is not possible to step outside history and look back at the past objectively. Understanding can only be possible with historical awareness; with historical awareness, everyone has a preunderstanding of the topic in question. Moreover, if preunderstandings are not recognized, there is a risk that understanding will be failed or meaning will be misjudged. The preunderstandings of the phenomenon should be visited time and time again and reflected upon during the process of gaining understanding.[22]

Participants

The participants were recruited from two hospital psycho-geriatric units and one hospital neurological unit. The medical staff at the units was given written information about the study and was asked to inform actual participants (family caregivers of individuals with FTD) about the study and ask if they were interested in participating. The inclusion criterion was a close relationship during the pre-diagnostic stage of FTD with a person later diagnosed with FTD. The participants returned the information letters to the main researcher with confirmation about interest in contributing to the study or with a refusal to participate in the study. The participants who wanted to contribute also added their phone numbers in the returned letter. In all, 16 persons were informed and agreed to participate in the study, but two of them could not participate for personal reasons. Fourteen people who were currently living or who had lived with a person with a diagnosis of FTD participated in the study. The participants had different relationships with the person with FTD and there was a variation in years past between observation of the earliest symptoms of FTD and the set FTD diagnosis (Table 1).

Interviews

The main researcher contacted the participants by phone after receiving the consent letters and the arrangements for the interviews were made in line with the participants' wishes. One interview took place at an office at a hospital, and one took place at a conference room at a hotel, but the rest of the interviews took place in the homes of the participants. The participants were interviewed by the main researcher and asked to narrate their experiences with the early stage of FTD. A semi-structured interview guide was used. This interview guide was developed for the study by the researchers, on the bases of literature review. The first question was: "Could you please tell me about the first time you experienced that your loved one had changed and what it meant to you?" with the following sub questions: "Could you please describe the changes?", "Could you please tell me more about your experience of the changes?", and "Could you please tell me what did the changes meant to you?" The interviews were estimated to last about 60 min, but they all lasted from 60 to 120 min. The participants were eager to tell their stories and had rich information, especially considering the initial question. All interviews were

Table 1
Participants and their loved ones.

Nr	Relationship to person with FTD	Gender of person with FTD	Age at earliest FTD symptoms observed in person with FTD	Age at FTD diagnosis in person with FTD	Years between observation of earliest symptom of FTD and FTD diagnosis
1	Daughter	M	55	67	12
2	Husband	F	45	47	2
3	Wife	M	65	69	4
4	Husband	F	67	67	0
5	Husband	F	64	67	3
6	Husband	F	61	64	3
7	Husband	F	45	55	10
8	Brother	F	65	70	5
9	Daughter	M	62	63	1
10	Wife	M	64	68	4
11	Wife	M	57	67	10
12	Close friend/former cohabitant	M	68	76	8
13	Daughter	M	66	70	4
14	Daughter	F	60	68	8
Relationships summarized	**%**				
Husband	35.72				
Wife	21.43				
Close friend/cohabitant	7.14				
Siblings	7.14				
Child	28.57				

Descriptions of participants' relationships to the persons with FTD. Descriptions of the loved ones with FTD: gender, age at earliest FTD symptoms, age at FTD diagnosis, and years between first symptoms and FTD diagnosis. Relationships summarized into percentages.

recorded and transcribed verbatim by the main researcher. The transcribed material was read through by all researchers in the study.

Ethical considerations

The participants were carefully informed that the interviews could trigger strong emotions that could emerge during or after the interview. If they needed support, they were told to contact the main researcher who is a registered nurse with specialization in psychiatry and several years of experience in psychiatric outdoor patients. The study was approved from the regional ethical committee in 2015 (ref. nr: REK midt 2015/847).

Text analysis

The four cyclical steps outlined by Fleming et al. (2002) inspired the analysis of the interview texts; (1): gain an understanding of the text as a whole, (2): identification of themes, (3): expanded understanding of the whole text and (4): Identification of passages.[22] According to Gadamer, analysis of an interview text needs to follow he hermeneutic movement; from the whole to the part and back to the whole.[22]

In the first step, the main researcher reflected upon her preunderstanding of the research question: how does family care givers experience the pre-diagnostic stage of FTD? The preunderstanding was that the family caregivers of persons with frontotemporal dementia do experience noticeable changes in their loved ones a long time before FTD has been diagnosed. All researchers separately read all the interviews as a whole text. The main researcher reviewed and wrote the fundamental meaning of the text as a whole, and this was read and reviewed by all the researchers.

In the second step, the main researcher gained an overall understanding of each text unit. Every sentence or section was investigated to expose its meaning in understanding of the research question. During this process, several meaning units were identified. The whole text and its meaning units were read by all the researchers and grouped into sub-themes. In the next stage, a main theme was made based upon the sub-themes. The sub-themes were reflected upon in the light of the main researcher's preunderstandings. Every section or sentence was then related to the meaning of the whole text, which expanded the sense of the text as a whole. The final step involved identifying passages that seemed to be representative of the shared understandings of the participants and the researcher. This multistep process was carried out several times during the analysis. The participants' perspectives were represented in the text as clearly and closely as possible and direct quotations were included.

Results

The main theme in our study was that the participants experienced the pre-diagnostic stage of FTD as a process with different steps of changes in the relationship with the loved one. This main theme was built upon the following subthemes: (a) becoming distant, (b) becoming insecure, (c) becoming devastated and (d) becoming a stranger. These steps of changes did not always occur in the same order in the participants.

Becoming distant

The process of changes in the interpersonal relationship with their loved one most often started with an experience of distance. An interpersonal relationship in this study is understood as a strong, deep, or close association between two or more people. In this study, the context of an interpersonal relationship was mainly intimate relationships (marital or romantic), but also family relationships like parent-child and sibling.

At first, the participants usually started experiencing almost unnoticeable changes in the relationship with their loved one, often in the form of increasing silence and apathy. The silence and apathy especially contributed to the experience of disconnection and distance in the relationship. Their loved one could seem uninterested in daily conversations, get more easily offended or irritated, or be more silent than usual. “He changed in the way he responded to me. . .he got easily offended and seemed agitated and a bit paranoid.” This feeling of disconnection in the relationship resulted in irritation or a subtle feeling that something didn't feel right. “We (the family members) were wondering about her, if there really was something wrong with her. She sometimes seemed disoriented, her personality changed, and she became so silent.”

These changes were not interpreted as a symptom of disease but rather often understood as due to natural causes, such as part of an aging process, stress, or just a downturn period in the relationship. “He did not take part in conversations like he used to, he did not have any input, and he withdrew. But we thought this was because he had bad hearing and did not manage to follow the conversation. I thought he was just getting old.”

The changes could also be experienced as recognizable symptoms from earlier periods of psychiatric or somatic illness. “She had periods of depression and fatigue earlier in her life, and I sometimes wonder if the frontotemporal dementia started already then.”

Becoming insecure

For most of the participants, the experience of distance gradually blended into an experience of insecurity about the situation. The changes in their loved one gradually became more noticeable, with he or she losing personal abilities or lessening personal activities, such as being active and social and losing interest in hobbies and even family. The participants found this strange, frightening, and irritating. Still, the changes were difficult to pinpoint and explain to others, and several participants also felt ashamed about the behavior of their loved one. Many of the participants talked to close friends or other family members about their concerns. Often, the affected person did not see the changes in himself or herself, which made it difficult to talk about it and also to make the person go see a doctor. This resulted in insecurity about the situation. “So I talked to my own doctor. I tried to explain the symptoms, and the doctor asked if we had problems in our marriage. I told him no and tried to explain a bit more, but I found it kind of embarrassing. I started to wonder if I was exaggerating. Nothing came of the visit to the doctor.”

Some of the participants experienced denial. In retrospect, they see that they subconsciously understood that something was wrong, but they tried to avoid thinking about it or talking about it with their loved one. “At first I didn't take any action, because I didn't want anything to be wrong with her. I don't know. I was in denial. I knew something was wrong, but I didn't know what it was. Maybe it was wrong of me. I have struggled with guilt. Could I have done anything? Could this have been avoided? Should I have seen something earlier? Should I have taken action earlier?”

Becoming devastated

As the helplessness of the loved one increased, the participants felt increasingly worried about the safety of their loved one. For a few of the participants, being devastated was their first step in the process of losing their loved one, as this was their first experience of changes in their loved one. This was particularly the case for the participants who experienced only a few years between observation of the earliest symptom of FTD and a set FTD diagnosis. A loss in ability of taking

care of oneself was commonly seen, particularly in personal hygiene. Even if the loved one had been neat and tidy earlier, it did not seem important to take a shower anymore. In some cases, the participants had to force their loved one to take a shower, which resulted in conflict and feelings of guilt. This was a devastating and exhausting situation. The participants who did not live with the person with FTD experienced that their loved one looked sloppy and unkempt when they came at visit. There were often clear signs of a lack of self-maintenance, such as overgrown nails and hair, rotten teeth, and bruises. In some cases, the participants also experienced their loved one wandering around outdoors or not being possible go get in touch with the person for longer periods of time. This led to feelings of concern, helplessness, and devastation in the participants. They also experienced a lack of help from health services because the person with FTD refused to receive assistance or left the house before health services came to visit. "The house started to decline. . . He did not clean. It smelled horrible inside the house. He did not turn the stove on, it was freezing cold, and he had no lights on. The community care tried to help him at first, but he was so aggressive toward them. I was worried sick; it was exhausting."

Several dangerous situations emerged because of the person's loss of abilities, such as driving, which became hazardous. The loss of skills and functions regarding cooking also led to potentially dangerous situations, such as fire or food poisoning. The participants experienced these dangerous situations with irritation, fear, and sometimes anger. In the wake of these situations, the participants were worried that it would happen again, which triggered catastrophic thoughts and insomnia. The participants struggled with leaving their loved one home alone when they went to work, which resulted in taking sick leave from work and sometimes even early retirement.

Some participants experienced serious behavioral and personality changes in their loved one, such as inappropriate laughter, sexualized behavior, jealousy, anger, physical abduction, shoplifting, abuse of alcohol, and wasteful spending. It was devastating to when their loved one, who had been modest and patient, suddenly became aggressive and abusive. Their loved one's behavioral and personality changes led to disgust, concern, irritation, fear, confusion, frustration, guilt, and catastrophic thoughts in the participants. "My wife and I were traveling. She got so depressed; she was not herself. Suddenly, I noticed that she drank alcohol in secret and that she had stolen alcohol from the tax-free shop."

Becoming a stranger

The last step in the process of the pre-diagnostic stage of FTD was the experience of becoming a stranger in the relationship. The loved one became a stranger due to these changes in behavior and personality and took on a different role in the relationship. The participants experienced that their loved one, once a person with interests, hobbies, and very good skills in everyday living, had lost an important part of themselves, the part that constituted them as a person. Several participants felt like they were living with a complete stranger. This was a devastating and horrible experience for the participants and resulted in tremendous feelings of guilt. As the person with FTD started to change and became increasingly helpless, the participants were forced to take on a new role in the relationship: a caregiver role. "I could not use him as a conversation partner anymore because he didn't understand in what way he could help me when I was struggling with something. It is a completely different relationship."

The role of caregiver was described as burdening by the participants. Some of the participants had to take on a parental role for their parent. " My mother lost her love and care for me. She was rude to me and made fun of me. It was horrible. You kind of expect your mother to feel love for you your whole life. Instead I had to be the parent for my mother."

This burden resulted in exhaustion and sometimes led to depression. The loved one had no insight in the fact that he or she had undergone changes in personality or behavior and did not want to talk about it at all or became irritated or angry if the participant tried to talk about it. "If I tried to confront her with her shoplifting and drinking, she just got angry with me. She said I was mean. She denied everything. I found it awful. It was horrible." In some cases, a need to have space between the person with FTD and the participant emerged even if the relationship had been positive and close earlier. This created conflicting feelings due to the need for space on one hand and a sense of duty on the other hand.

Discussion

The aim of this study was to explore the family caregivers' experiences of the pre-diagnostic stage of FTD.

The participations in our study described the early stage of frontotemporal dementia as changes in their interpersonal relationship with the loved person, because of personal and behavioral changes. It was experienced as a complex and demanding situation, characterized by the emotions of shame, irritation, guilt, exhaustion, and fear. The early changes were subtle and often misinterpreted or denied by the family caregivers and were difficult to explain.

As far as we know, only one study has have explored family caregivers experiences of the pre-diagnostic stage of FTD.[15] However, studies argue that the most difficult period for the family caregiver of a person with dementia is the period before the dementia diagnosis. The changes in personality and communication are difficult to handle, and the caregivers do not have an explanation for these changes. The changes in marital roles are particularly distressing.[23] During this period, the doubt is often followed with hope that the changes would pass or some natural explanation would emerge.[24] This is in line with the findings in our study, where the participants first experienced almost unnoticeable changes in the communication and relation with their loved ones. Later on, as these changes got more noticeable, the participants felt insecure about the situation and sometimes went in denial.

A study of Massimo et al. (2013) shows that the relationship in spouses often undergo a sudden shift in FTD, as a result of loss of meaningful connection with the spouse.[13] Our study shows a more gradual change in the relationship. The first changes described under "becoming distant" did resulted in irritation but was explained by the participants as due to natural changes such as part of an aging process, stress, or just a downturn period in the relationship.

In FTD, changes in the patient's behavior and changes in the interpersonal relationship between the spouse and the caregiver is associated with caregiver depression[21] and is challenging for maintaining a healthy marital bond.[25] The behavioral changes leads to an absence of meaningful connection to the loved one and may create feelings of isolation and anger[13] This is recognizable from our study, in the findings "becoming devastated" . As the behavioral and personality changes in the loved one became more noticeable and serious, the participant described disgust, concern, irritation, fear, confusion, frustration, guilt, and catastrophic thoughts.

Caregivers often experience loss of self-identity and the role changes in the relationship in FTD.[13] This is in line of findings in our study. The participant describes the experience of "becoming a stranger" in the relationship with their loved one. Several participants felt as if they lived with a total stranger. Their loved one had lost their personality and what once constituted them as a person. The roles of being a spouse, child, close friend or sibling changed into being a caregiver as the loved one changed and needed more support in the everyday life.

Studies show that family caregivers in early onset dementia get concerned about the changing roles in the family as the dementia

progress.[13, 16] and that adult children experience that the main caregiver (mother or father) avoids or withdraws from the situation.[26] Spouses and child caregivers may experience similar levels of burden.[27] Four of the participants in our study were grown up daughters of a loved one with FTD. These participants experienced that they had to take on a parental role for their parent, which was demanding and distressing.

In our study, the family caregivers did not interpret the early signs of FTD as signs of a dementia disease. This is in line with other studies which shows that in the early stage of FTD, the symptoms might lead to a misdiagnosis of depression,[19] midlife crisis, marital conflict, stress, menopause,[5] manic psychosis, obsessive-compulsive disorder, or sociopathic personality disorder.[28] The most frequent misdiagnosis of bv-FTD is major depression, where the family caregivers have interpreted the apathy, loss of interest, and social withdrawal as depression.[11] Some of the participants in our study tried to explain the symptoms to medical staff, but did not feel as if it was taken serious. Studies show that this is not uncommon. Physicians may be unaware that neurodegenerative disease can affect younger persons. This leave the family caregivers in a frustrating, uncertain, and confusing situation.[28] Also, it is not unusual for couples to seek family counseling or divorce during the pre-diagnostic stage of FTD.[28] Several participants in our study experienced lack of insight in their loved ones. Most of the patients with FTD do not complain of any symptoms, behavioral changes described by family caregivers are often unspecific, the patients may perform normally on neuropsychological tests, and structural imaging abnormalities may be subtle.[11]

Blandin and Pepin (2016) have developed a theoretical model of pre-death grief in dementia caregivers. The model encompasses three states: (1) the separation state, (2) the liminal state, and (3) the re-emergence state.[29] The separation state is characterized by the losses that a family caregiver experiences in their loved. It is difficult to acknowledge the loss, as the family caregiver may not recognize the changes, may resist or deny the changes, or be too emotionally drained to see the changes.[29] Our study supports these findings, which describes both loss of emotional connection with the loved one and a denial of changes in the participants. The liminal state is characterized by being in between a previous situation and an emerging situation. It encompasses an experience of ambiguous loss and recession of the known self, which precedes physical death.[29] In the findings of our study, this state appears in the subthemes of becoming devastated and becoming a stranger. According to Blandin and Pepin (2016), tolerating the painful emotions in this state enables the grief process to unfold, and there is an opportunity to adapt to the new, emergent situation. This naturally moves the caregivers into the final state of the grief model: the state of re-emergence. In this state, it is possible for the family caregiver to adapt to the new life situation and to the reality of the loss. In general, during the grief process, adaption is a goal that signals resolution.[29] However, the participants in our study remained in the painful liminal state for up to 12 years before they learned the actual diagnosis.

This may constitute the biggest difference between the pre-diagnostic stage of FTD and other dementias: a delay of diagnosis and a delay of the state of re-emergence.

Methodological consideration

The design of our study made us able to gain a deeper understanding in a less-explored subject: family caregiver's experiences during the pre-diagnostic stage of FTD. The participants experienced the pre-diagnostic stage of FTD as a process with different steps of changes in the relationship with the loved one. The participants experienced these steps in different order.

The participants had different relationships with the person with FTD and they all were in different stages in a mourning process during the interviews. The differences in relationships and the age of the participants may have contributed to different experiences during the pre-diagnostic stage of FTD. Some of the participants were still living with their loved one, some of the participants had experienced the death of their loved ones, and, in some cases, the loved one had moved to an institution. This may be the reason why the participants experienced the different steps in the process in a different order.

All participants were emotionally affected by their loss during the interviews. This may have influenced their narratives, leading their focus to the present situation of their loved ones or the mourning process, instead of the early signs of disease. However, each interview was rich in details on early signs of FTD and the participants' experiences of it.

This interpretation is only one of several possible ones. The findings in our qualitative study cannot be generalized in a statistical sense, but we argue that they are transferable to other family caregivers of persons with FTD. This study can be used for development of competence regarding early signs of FTD and development of competence regarding the difficult and complex task of early and correct FTD diagnosis.

Conclusion

The family caregivers in our study experienced changes in their loved one before actual diagnosis. The changes were not initially interpreted as signs of disease, but eventually, these changes led to major concerns. Still, the changes were difficult to pinpoint and describe to others. The devastating and exhausting character of the process, the difficulties of describing the subtle symptoms and a lack of awareness in clinicians may contribute to the delay in diagnosis. In other dementias, like Alzheimer's disease and vascular dementia, the symptom of memory loss often raises the suspicion of dementia. In these cases, the family caregivers may be prepared for a dementia diagnosis, and the symptoms may be easier to explain to a clinician. Our study shows that is important for clinicians to be pay attention when spouses or other family members are concerned about personality and behavioral changes or loss of functions in a loved one, even if the symptoms are difficult to pinpoint and describe. The awareness of frontotemporal dementia should be raised, especially among general clinicians, but also among specialists.

Conflicts of interest and funding

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Paper 3

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Original Research Article

Anxiety and Depression as Risk Factors in Frontotemporal Dementia and Alzheimer's Disease: The HUNT Study

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Keywords
Longitudinal studies · Case-control studies · Dementia · Frontal lobe · Neurodegenerative diseases · Epidemiology · Psychiatric symptoms

Abstract
Background: The roles of both anxiety and depression as risk factors for frontotemporal dementia (FTD) and Alzheimer's disease (AD) have not been previously investigated together. ***Objective:*** To study anxiety and depression as independent risk factors for FTD and AD. ***Methods:*** Eighty-four patients with FTD and 556 patients with AD were compared with 117 cognitively healthy (CH), elderly individuals. Both cases and controls were participants in the second Health Study of Nord-Trøndelag (HUNT2) from 1995 to 1997, in which depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS). ***Results:*** Significant associations were found between anxiety and FTD and between depression and AD. A significantly increased risk of developing FTD was observed in patients who had reported anxiety on the HADS (p = 0.017) (odds ratio [OR]: 2.947, 95% confidence interval [CI]: 1.209–7.158) and a significantly increased risk of developing AD was observed in patients who had reported depression on the HADS (p = 0.016) (OR: 4.389, 95% CI: 1.311–14.690). ***Conclusion:*** Our study findings suggest that anxiety and depression may play different roles as risk factors for FTD and AD.

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Background

The number of individuals with dementia worldwide is estimated to be over 45 million and is predicted to triple by 2050 [1]. The identification of modifiable risk factors may lead to viable prevention strategies [2]. Frontotemporal dementia (FTD) refers to clinical syndromes caused by neurodegeneration in the frontal or temporal lobes of the brain. FTD consists of three clinical subtypes: (1) behavioral variant FTD (bvFTD), which is characterized by changes in personality and behavior; (2) non-fluent variant primary progressive aphasia, which is characterized by deficits in speech and grammar, and (3) semantic variant primary progressive aphasia, which is characterized by deficits in semantic knowledge and naming [3, 4].

FTD accounts for 10% of all occurring dementia cases and is a leading cause of early-onset dementia, i.e., onset before the age of 65 years. Early symptoms often include insidious behavioral and personality changes and problems with language [5, 6]. The symptoms of behavioral and personality changes are similar to symptoms seen in psychiatric disorders and this often leads to an incorrect initial diagnosis [7]. About 60% of FTD cases are diagnosed between the age of 45 and 60 years [8, 9]. Modifiable risk factors in FTD have been investigated far less than in Alzheimer's disease (AD) and vascular dementia and although some studies have found associations between FTD and diabetes mellitus [10], head trauma [11–13], education level [14], and autoimmune disease [15], knowledge on modifiable risk factors in FTD is considered sparse [16].

AD accounts for 60–80% of all cases of dementia [17], and these patients display early symptoms of memory problems, apathy, as well as depression, and later communication problems, confusion, disorientation, behavioral changes, and difficulties with speech, swallowing, and walking [8]. Several risk factors for AD have been researched and established, including hypertension, diabetes, hypercholesterolemia, body mass index (BMI), education, and socioeconomic status, along with depression, affective disorders, social network, and social engagement [18–22].

Anxiety and depression are common mental disorders among the general population [23, 24]. Symptoms of depression and anxiety are graded by their severity, duration, and functional impairment, and a diagnosis of anxiety or depression requires a clinical assessment [25]. Depression is a common disorder in the elderly population, and studies performed in the last decade have implied an increasing prevalence of depression with age [26, 27]. Anxiety is harder to assess in elderly individuals, but studies have found it to occur less often than depression and that severe forms are also less common in the elderly [28].

A few studies have compared risk factors in FTD and AD, finding that patients with FTD were less likely to have hypertension [14, 29], had a lower prevalence of cerebrovascular risk factors [29], were younger and more educated, and were more likely to have a positive family history of dementia than patients with AD [14]. Not only is knowledge of modifiable risk factors for FTD sparse, there has also been a lack of longitudinal studies assessing modifiable risk factors and their impact on premorbid FTD and AD. The aim of this longitudinal population-based case-control study was to investigate the role of anxiety and depression as modifiable risk factors in FTD compared with in AD.

Methods

Study Population

In this population-based, longitudinal nested case-control study, the study population comprised of 84 individuals with FTD, 556 individuals with AD, and a control group of 117

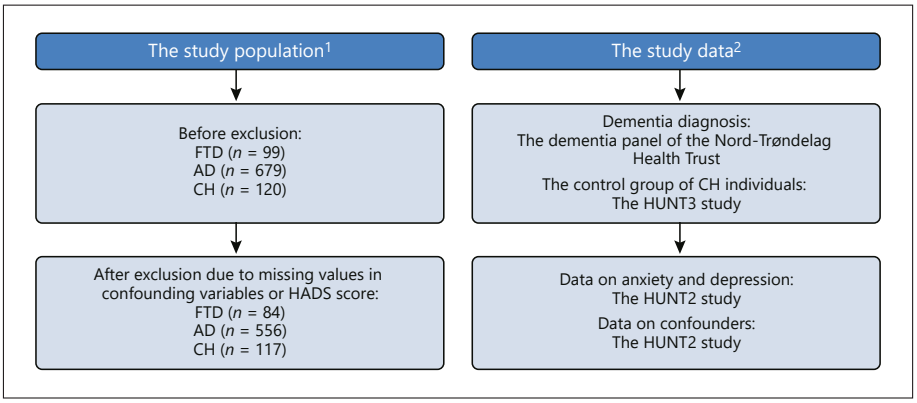

Fig. 1. Study population and data. [1] Study population before and after exclusion. [2] Study data: dementia diagnosis, assessments of anxiety and depression, and confounders. FTD, frontotemporal dementia; AD, Alzheimer's disease; CH, cognitively healthy.

verified cognitively healthy (CH) elderly individuals (Fig. 1). Cases with a diagnosis of FTD and AD were identified from the Dementia Register of the Nord-Trøndelag Hospital Trust [30] (Fig. 1). This Dementia Register consists of data collected from a Nursing Home Dementia Register and a Hospital Dementia Register.

The CH control group was selected from a follow-up project on memory and intelligence after HUNT3 between 2010 and 2011 [31] (Fig. 1). During this project, the individuals were examined by a neuropsychologist and categorized as CH [31].

All cases and controls in our study had participated in the second study of the Health Study of Nord-Trøndelag (HUNT2) between 1995 and 1997 and completed the Hospital Anxiety and Depression Scale (HADS). In the HUNT2 study, participants underwent a brief medical examination and were asked to complete questionnaires including physical and mental health-related items. The HUNT2 study has been described in more detail previously [32].

FTD and AD cases and CH individuals with valid HADS scores were included in our study. Cases and controls with missing data or nonvalid HADS scores were excluded (Fig. 1).

Dementia Diagnosis

The Hospital Dementia Register includes data on dementia diagnosis collected retrospectively (1995–2010) and prospectively (2010–2017) by the Nord-Trøndelag Hospital Trust. Diagnosis is performed according to national and international guidelines by specialists in geriatric and psychogeriatric medicine, and is based on patient history, caregiver history, clinical examinations, neuropsychological assessments, blood samples, and brain imaging [30].

The Nursing Home Dementia Register includes data on dementia diagnosis collected from nursing homes in Nord-Trøndelag during 2010–2011. Diagnostic data were collected by trained nurses by conducting several tests measuring cognitive function, neuropsychiatric symptoms, depression symptoms, quality of life, caregiver distress, and personal activities of daily living. Using the available information, two physicians with wide clinical and research experience independently diagnosed mild cognitive impairment, dementia syndromes, and dementia subtypes. If there was any discrepancy, a third expert was consulted [30].

Anxiety and Depression Measurements

Data on self-reported symptoms of anxiety and depression were extracted from the HUNT2 study, in which the HADS was used to measure depression and anxiety (Fig. 1). The HADS consists of 14 items covering 2 subscales, with 7 items for anxiety (HADS-A) and 7 for depression (HADS-D). Each item is scored on a 4-point Likert scale (0: not present, 3: fully present). The subscale sum scores have a minimum of 0 and maximum of 21. Snaith and Zigmond [33] categorized the HADS-A and HADS-D subscale scores of 0–7 as normal, 8–10 as mild disorder, 11–14 as moderate disorder, and 15–21 as severe disorder. In this study, we included HADS scores where at least five out of the seven questions on both HADS-D and HADS-A were answered. Those who filled in 5 or 6 items were included and their score was based on the sum of completed items multiplied with 7 of 5 or 7 of 6.

In the FTD group, 3 cases had answered 5 out of 7 items and 13 cases had answered 6 out of 7 items on the HADS-A. No cases had answered 5 out of 7 items and 5 cases had answered 6 out of 7 items on the HADS-D. In the AD group, 34 cases had answered 5 out of 7 items and 97 cases had answered 6 out of 7 items on the HADS-A. Sixteen cases had answered 5 out of 7 items and 64 cases had answered 6 out of 7 items on the HADS-D. In the CH group, 7 controls had answered 5 out of 7 items and 18 controls had answered 6 out of 7 items on the HADS-A. One control had answered 5 out of 7 items and 7 controls had answered 6 out of 7 items on the HADS-D. We used a score of 8 or above as the cutoff indicating a probable case of anxiety or depression [34].

Confounders

Data on confounders were extracted from the HUNT2 study. Based on previous studies, we selected variables that might confound the associations between anxiety/depression and FTD/AD. Confounders can influence both the dependent variable and the independent variable, causing a spurious association. Therefore, the confounders chosen for this study were gender, age at participation in the HUNT2 study, heart disease, diabetes, metabolic disorder, hypertension, smoking, and obesity. Heart disease was ascertained if participants indicated they had experienced angina pectoris or heart attack. Similarly, diabetes and metabolic disorders (hypothyroidism or hyperthyroidism) were determined if responses were positive. Hypertension was determined if participants had an average diastolic blood pressure of 90 mm Hg or more. Patients with a BMI of 30 or higher were classified as obese. Tobacco use was categorized as never smoked on a daily basis, previous daily smoker, or daily smoker. Owing to missing data, potential confounders, such as education, brain disease, and alcohol use, were not included in the final analysis.

Statistical Analysis

Datasets from the Dementia Register of the Nord-Trøndelag Hospital Trust and the HUNT2 study were merged using the personal identification number assigned to all Norwegian citizens. The personal identification number was then replaced with an anonymous project identification number before the merged dataset was made available to the researchers. We evaluated the association between anxiety and depression, measured by HADS in the HUNT2 study, and the later development of FTD and AD using multivariable logistic regression. Three analyses were performed separately: (1) analysis of FTD versus CH individuals; (2) analysis of FTD versus AD; and (3) analysis of AD versus CH individuals. All three analyses were performed in four steps: (1) entering anxiety only as the variable; (2) entering depression only as the variable; (3) entering anxiety and depression as variables; and (4) entering anxiety and depression as variables and adjusting for the potential confounders of age, gender, heart disease, diabetes, hypertension, metabolic disease, smoking, and obesity. The analyses were performed using SPSS version 25.

Table 1. Characteristics of the study population

	FTD (n = 84)	AD (n = 556)	CH (n = 117)
Female, %	66.7	68.7	53.0
Mean age at participation in the HUNT2 study, years	67.7	71.8	61.2
Mean age at dementia diagnosis, years	74.4	79.2	
Risk factors, %			
Heart disease	15.5	16.0	6.8
Diabetes	3.6	5.0	1.7
Hypertension	32.1	29.5	29.9
Metabolic disease	11.9	8.3	6.0
Smoking	53.5	44.9	57.2
Obesity	26.2	18.0	12.8
Anxiety	29.3	21.1	8.8
Depression	13.0	13.9	2.7

The study was conducted at the Namsos Hospital, Nord-Trøndelag Health Trust, with approval from the Regional Etisk Komite (REK), the Norwegian ethics committee. Participating patients gave written consent to take part in the HUNT2 and HUNT3 studies [35].

Results

Characteristics of the Study Population

Compared with the CH group, the AD and FTD groups were older at participation in the HUNT2 study and were more likely to have heart disease, diabetes, metabolic disease, obesity, anxiety, and depression. Compared with the AD group, the FTD group was younger at participation in the HUNT2 study and at time of diagnosis. The FTD cases were also more likely to have hypertension, metabolic disease, obesity, as well as anxiety and to smoke (Table 1). All cases in the FTD group received their dementia diagnosis after the year 2000. In the AD group, 26 cases received their dementia diagnosis between 1995 and 1999 and the remainder after the year 2000.

FTD Compared to CH Individuals

In the initial analysis entering only anxiety as a variable, a significant association between anxiety and developing FTD was seen (p = 0.000; odds ratio [OR]: 4.303, 95% confidence interval [CI]: 1.925–9.622) compared with the CH group. When entering only depression as a variable, a significant association between depression and developing FTD was also seen (p = 0.012; OR: 5.473, 95% CI: 1.454–20.599). When both anxiety and depression were entered as variables, a significant increase in the risk of developing FTD was observed in patients who had reported anxiety on the HADS (p = 0.017; OR: 2.947, 95% CI: 1.209–7.158). There was no significant association between depression and risk of developing FTD (p = 0.151; OR: 2.879, 95% CI: 0.681–12.176). The findings regarding anxiety were consistent after adjusting for the potential confounders (p = 0.045; OR: 2.797, 95% CI: 1.024–7.642) (Table 2).

FTD Compared to AD

In the initial analysis entering only anxiety as a variable, no significant association between anxiety and developing FTD was seen (p = 0.099; OR: 1.549, 95% CI: 0.920–2.607) compared with the AD group. When entering only depression as a variable, no significant

Table 2. Comparison between FTD and CH groups

	p value	OR	Lower (95% CI)	Upper (95% CI)
Anxiety[a]	0.000	4.303	1.925	9.622
Depression[b]	0.012	5.473	1.454	20.599
Anxiety and depression[c]	0.017	2.942	1.209	7.158
	0.151	2.879	0.681	12.176
Adjusted analysis[d]				
Anxiety	0.045	2.797	1.024	7.642
Depression	0.100	3.925	0.771	19.982
Age at participation in HUNT2	0.000	1.095	1.049	1.143
Gender	0.243	0.651	0.316	1.339
Heart disease	0.076	2.716	0.902	8.175
Diabetes	0.745	0.687	0.071	6.611
Hypertension	0.876	1.060	0.511	2.196
Metabolic disease	0.484	0.929	0.756	1.142
Smoking	0.080	1.525	0.950	2.447
Obesity	0.027	2.648	1.119	6.268

Anxiety and depression as risk factors for FTD compared with CH individuals. CI, Confidence interval; OR, odds ratio. [a] Anxiety entered as variable. [b] Depression entered as variable. [c] Anxiety and depression entered as variables. [d] Anxiety, depression, and confounders entered as variables.

association between depression and developing FTD was seen ($p = 0.828$; OR: 0.924, 95% CI: 0.453–1.883) compared with the AD group. When both anxiety and depression were entered as variables, there were no significant associations between anxiety and developing FTD ($p = 0.146$; OR: 1.592, 95% CI: 0.851–2.979) or between depression and developing FTD ($p = 0.490$; OR: 0.751, 95% CI: 0.333–1.694) compared with AD. No significant associations for anxiety or depression were seen after adjusting for potential confounders (Table 3).

AD Compared to CH Elderly

In the initial analysis entering only anxiety as a variable, a significant association for developing AD was seen ($p = 0.003$; OR: 2.778, 95% CI: 1.404–5.498). When entering only depression as a variable, a significant association for developing AD was also seen ($p = 0.003$; OR: 5.922, 95% CI: 1.829–19.181). When both anxiety and depression were entered as variables, a nearly significant increase in the risk of developing AD was observed in patients who had reported anxiety on the HADS ($p = 0.054$; OR: 2.009, 95% CI: 0.988–4.087). There was also a significant association between depression and the risk of developing AD ($p = 0.016$; OR: 4.389, 95% CI: 1.311–14.690). The nearly significant association for anxiety was reduced ($p = 0.114$; OR: 1.967, 95% CI: 0.850–4.554) after adjusting for potential confounders. The findings regarding depression were consistent after adjusting for potential confounders ($p = 0.032$; OR: 4.494, 95% CI: 1.139–17.731) (Table 4).

Discussion

This study investigated the association between anxiety and depression and the risk of receiving a diagnosis of FTD or AD. Anxiety was more likely to be reported at baseline in the HUNT2 study among those who later developed FTD than in the CH control group. Conversely,

Table 3. Comparison between FTD and AD

	p value	OR	Lower (95% CI)	Upper (95% CI)
Anxiety[a]	0.099	1.549	0.920	2.607
Depression[b]	0.828	0.924	0.453	1.883
Anxiety and depression[c]	0.161 0.439	1.538 0.734	0.842 0.335	2.806 1.608
Adjusted analysis[d]				
Anxiety	0.146	1.592	0.851	2.979
Depression	0.490	0.751	0.333	1.694
Age at participation in HUNT2	0.000	0.945	0.916	.975
Gender	0.801	1.074	0.617	1.868
Heart disease	0.721	0.962	0.778	1.189
Diabetes	0.371	0.509	0.116	2.232
Hypertension	0.890	1.014	0.829	1.241
Metabolic disease	0.615	0.958	0.809	1.133
Smoking	0.585	1.099	0.782	1.545
Obesity	0.670	0.967	0.828	1.129

Anxiety and depression as risk factors for FTD compared with AD. CI, Confidence interval; OR, odds ratio. [a] Anxiety entered as variable. [b] Depression entered as variable. [c] Anxiety and depression entered as variables. [d] Anxiety, depression, and confounders entered as variables.

Table 4. Comparison between AD and CH individuals

	p value	OR	Lower (95% CI)	Upper (95% CI)
Anxiety[a]	0.003	2.778	1.404	5.498
Depression[b]	0.003	5.922	1.829	19.181
Anxiety and depression[c]	0.054 0.016	2.009 4.389	0.988 1.311	4.087 14.690
Adjusted analysis[d]				
Anxiety	0.114	1.967	0.850	4.554
Depression	0.032	4.494	1.139	17.731
Age at participation in HUNT2	0.000	1.166	1.129	1.203
Gender	0.029	0.559	0.332	0.943
Heart disease	0.104	2.139	0.856	5.343
Diabetes	0.379	2.005	0.426	9.430
Hypertension	0.185	0.732	0.462	1.161
Metabolic disease	0.161	0.972	0.934	1.011
Smoking	0.222	1.247	0.875	1.778
Obesity	0.160	1.412	0.872	2.287

Anxiety and depression as risk factors for AD compared with CH individuals. CI, Confidence interval; OR, odds ratio. [a] Only anxiety entered as variable. [b] Only depression entered as variable. [c] Anxiety and depression entered as variables. [d] Anxiety, depression, and confounders entered as variables.

depression was more likely to be reported at baseline in the HUNT2 study among those who later developed AD than in the CH control group. When FTD was compared with AD, no significant increase in the risk of developing FTD was observed in patients who had reported anxiety or in patients who had reported depression. To our knowledge, no previous studies have eval-

uated the association between both anxiety and depression together and the development of FTD. Thus, our finding that anxiety may be a risk factor for FTD needs further investigation.

Several studies have found depression to be a risk factor for AD [36–39] and for dementia in general [37, 40, 41]. Numerous mechanisms for the association between depression and the development of dementia have been proposed, such as vascular disease, alterations in glucocorticoid steroids, hippocampal atrophy, increased depositions of β-amyloid plaques, inflammatory changes, and deficits of nerve growth factors or neurotrophins [42]. Depression has also been linked to habits like smoking, obesity, and reduced regular physical activity, which are also cardiovascular risk factors [43]. Another suggested shared mechanism is that of inflammation and immune activation, which can be characteristic of depression and is also associated with an increased risk for all types of dementia [43]. Depression as a risk factor for dementia has been better investigated in late-life depression (age over 60 years and older) [42]. The few studies investigating the association between early-life depression and dementia have consistently found depression as a risk factor for dementia and unlikely to be solely a prodrome of dementia [42].

In the unadjusted analyses in our study, we found a nearly significant association between anxiety and the later development of AD. A previous study has also found a similar association [44]. Other studies have found prior anxiety to be a risk factor for dementia in general, including AD [18, 43–48]. Few hypotheses have been offered to explain the association between anxiety and dementia. One suggestion is that apolipoprotein E may be linked to anxiety as well as dementia [49]. Other mechanisms suggest that neuropeptides and the hypothalamic-pituitary-adrenal axis could be involved [48]. Another possible mediating factor could be the use of benzodiazepines, which may be prescribed as treatment for anxiety. In some studies, benzodiazepine use has been found as a risk factor for AD [50], but it remains unclear if this association is more than merely correlative.

In our study, there were no significant associations for either anxiety or depression when FTD cases were compared with AD cases. This may have several explanations. The FTD group was significantly smaller than the AD group. It is also possible that some of the FTD cases had AD, but with the type of neuropsychiatric symptoms seen in FTD. This is especially relevant for the FTD cases selected from the Nursing Home Dementia Register, which may have been in an advanced stage of AD at the time of formal dementia diagnosis. During the last stages of AD, the neuropsychiatric symptoms seen in FTD may occur.

Strengths and Limitations of the Study

The main strength of our study is its longitudinal, population-based, nested case-control design. Another strength is the use of a validated dementia diagnosis and data on anxiety and depression from the HADS [33, 51]. We were able to investigate risk factors measured in the HUNT2 years before the FTD and AD diagnoses were made. Furthermore, our study has a comparable number of FTD cases to other studies, where populations have varied from 61 to 129 cases [10–12, 14, 15, 29, 52, 53]. An exception was the study by Deutsch et al. [13] on head trauma as a risk factor for FTD, which had 1,016 FTD cases. A further advantage of our study was that in the multivariable analyses we were able to adjust for a large number of potential confounding factors.

There were also limitations to our study. Some of the dementia diagnoses in the Hospital Dementia Register were recorded retrospectively. Although most patients referred to hospitals were examined by multiple doctors who implemented standard routines, some files had missing data, which may have reduced the validity of some diagnoses [30]. The diagnosis of dementia in the Nursing Home Dementia Register was based on a review of data collected from patients, their family members, and their caregivers. However, two physicians with extensive clinical and research experience found the data sufficient to make a diagnosis

according to established criteria. The number of patients diagnosed with FTD was higher in the Nursing Home Dementia Register. FTD patients may need treatment and nursing home care earlier than those with AD. Diagnosing dementia specifically as FTD in patients living in nursing homes is more difficult than in those attending hospital outpatient clinics, although the dataset from the Nursing Home Dementia Register included information on symptoms early in the course of the disease. Further, AD patients will develop a behavior and symptoms similar to FTD patients later in disease and are therefore often incorrectly diagnosed with FTD [30]. Consequently, a possible misclassification of dementia type may have affected the point estimates in our study because the FTD group may have consisted of both FTD and AD cases. Additionally, the CH control group comprised individuals with healthy brains and may not have been truly representative of the general population.

The HADS is self-rated and scoring could be biased by the person's feelings at the time they filled out the questionnaire. There is also a possibility that some FTD or AD cases developed cognitive impairment before participation in the HUNT2 study. Filling out a self-rated questionnaire may be problematic for individuals with cognitive impairment because insight and the ability to quantify emotional states may be impaired. Understanding and interpretation of the questions in the HADS may also be subject to individual variation. However, previous studies have shown the HADS to be satisfactory in terms of internal consistency, factor structure, and intercorrelation [51].

Interpretation

Our results suggest that we can view anxiety and depression as differing risk factors for FTD and AD. The finding that anxiety was more often reported in premorbid FTD than in AD can be explained by a shared underlying psychiatric component, for example, the suggested relationship between apolipoprotein E, anxiety, and dementia [49], or the use of medications, such as benzodiazepines [50]. However, we cannot rule out the possibility that the anxiety symptoms reported on the HADS at baseline in the HUNT2 study are part of a prodromal phase in FTD. The identification of early prodromal states in FTD continues to pose challenges [54]. Studies have found that it can take from 5 to 10 years to make a correct diagnosis [55, 56], and our findings warrant more research to further explain the correlation between anxiety and FTD.

Another important finding was that depression was more often reported in premorbid AD than in CH controls. This suggests that depression symptoms, as reported on the HADS at baseline in the HUNT2 study, may be part of a prodromal phase of AD. AD develops slowly and the prodromal phase has been estimated to last from 1 year to more than 10 years [57]. Furthermore, AD and depression may be linked by vascular disease, alterations in glucocorticoid steroids, hippocampal atrophy, increased depositions of β-amyloid plaques, inflammatory changes, and deficits of nerve growth factors or neurotrophins [42], none of which are commonly seen in FTD.

Conclusion

Our study results suggested that prior anxiety is associated with a diagnosis of FTD and prior depression is associated with AD, after adjustment for other risk factors. Anxiety and depression as risk factors may play different roles in FTD and AD. Differences between FTD and AD in modifiable risk factors should be considered in future research, which requires a longitudinal design with long follow-up periods to clarify the consistency of earlier findings on modifiable FTD risk factors. Further research should also analyze genetic data to separate genetic and sporadic cases of FTD, providing further enlightenment of the possible relationships between modifiable and nonmodifiable risk factors for FTD.

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Statement of Ethics

The study was conducted at the Namsos Hospital, Nord-Trøndelag Health Trust, with approval from the Regional Etisk Komite (REK), the Norwegian ethics committee. Participating patients gave written consent to take part in the HUNT2 and HUNT3 studies.

Disclosure Statement

The authors have no conflicts of interests to declare.

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Paper 4

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Original Research Article

Smoking and Obesity as Risk Factors in Frontotemporal Dementia and Alzheimer's Disease: The HUNT Study

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Keywords
Longitudinal studies · Case-control studies · Dementia · Frontal lobe · Neurodegenerative diseases · Epidemiology · Psychiatric symptoms

Abstract
Background: Few studies have assessed smoking and obesity together as risk factors for frontotemporal dementia (FTD) and Alzheimer's disease (AD). ***Objective:*** To study smoking and obesity as risk factors for FTD and AD. ***Methods:*** Ninety patients with FTD and 654 patients with AD were compared with 116 cognitively healthy elderly individuals in a longitudinal design with 15–31 years between measurements of risk factors before the dementia diagnosis. ***Results:*** There were no associations between smoking and FTD (p = 0.218; odds ratio [OR]: 0.990; 95% confidence interval [CI]: 0.975–1.006). There were significant associations between obesity and FTD (p = 0.049; OR: 2.629; 95% CI: 1.003–6.894). There were significant associations between both smoking (p = 0.014; OR: 0.987; 95% CI: 0.977–0.997) and obesity (p = 0.015; OR: 2.679; 95% CI: 1.211–5.928) and AD. ***Conclusion:*** Our findings suggest that obesity is a shared risk factor for FTD and AD, while smoking plays various roles as a risk factor for FTD and AD.

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Introduction

Frontotemporal dementia (FTD) is considered to be a common cause of dementia in younger adults [1, 2], yet very few studies have investigated modifiable risk factors for FTD [3]. FTD is a neurodegenerative disease leading to loss of neurons in the frontal and/or temporal lobes in the brain [4–6]. This results in severe neuropsychiatric symptoms such as changes in behavior and personality and changes in language use [7, 8]. About 60% of FTD cases are diagnosed between the ages of 45 and 60 years [1]. No curative treatment for FTD exists today, but identification of modifiable risk factors may lead to viable prevention strategies [9].

Alzheimer's disease (AD) is the most common cause of dementia [10, 11]. Early symptoms are known to be memory deficits, apathy, and depression [11, 12]. Later symptoms include problems in communication, confusion, behavioral changes, and disorientation [11]. For AD, medical treatment may delay the progression of the disease, and modifiable risk factors have been extensively investigated [13].

Some studies have found associations between FTD and diabetes mellitus [14], head trauma [15–17], education level [18], autoimmune disease [19], and anxiety [20]. When it comes to AD, hypertension, diabetes, hypercholesterolemia, increased body mass index (BMI), lower education, lower socioeconomic status, depression, affective disorders, poor social network, lower social engagement, and smoking are all well-known risk factors [13, 21–25]. To our knowledge, very few studies have investigated modifiable risk factors in FTD compared with AD. It is important to investigate similarities and differences when it comes to modifiable risk factors for these diseases because the findings may aid researchers in exploring new concepts in prevention and treatment.

Tobacco use and obesity are among the leading risks for mortality in the world [26]. Smoking is a well-known risk factor for dementia [25, 27], and it has been hypothesized that it can lead to dementia indirectly through cerebrovascular disease, stroke, heart disease, increased total plasma homocysteine, atherosclerosis, and oxidative stress [25]. A decrease in smoking has been seen in some high-income countries, but the numbers of smokers are still increasing in many low- and middle-income countries [26].

Obesity is associated with an increased risk for dementia [13, 27, 28] by mechanisms that include insulin resistance diabetes, cardiovascular disease, hypertension, increased inflammation, and higher levels of cytokines [28]. The prevalence of obesity has been increasing for several years [29], with the highest average BMI in Europe, America, and the eastern Mediterranean countries [26].

The aim of this longitudinal population-based case-control study was to examine modifiable risk factors for FTD and to investigate the role of smoking and obesity as modifiable risk factors in FTD compared with AD.

Methods

Study Population

We performed a population-based, longitudinal nested case-control study. The study population consisted of 90 patients with FTD, 654 patients with AD, and a control group of 116 verified cognitively healthy (CH) elderly individuals (Fig. 1).

Cases with FTD and AD diagnoses were identified from the dementia register of North-Trøndelag Hospital Trust, Norway (Fig. 1). This dementia register consists of data collected from two registers: the Nursing Home Dementia Register and the Hospital Dementia Register [30]. The CH control group was selected from a follow-up project on memory and intelligence after HUNT3 between 2010 and 2011 [31] (Fig. 1). During this project, individuals were

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1984–1986	1995–2017	2010–2011	2017
Participation in HUNT1	Included in the Dementia Register (FTD and AD groups)	Included in a follow-up project (CH group)	Included in our study (FTD, AD, and CH groups)

The FTD patients, AD patients, and CH control individuals in our study first participated in the HUNT1 study in 1984–1986. Somewhere between 1995 and 2017, the FTD and AD patients were included in the dementia register after assessments that resulted in a dementia diagnosis. The CH control group was selected from a follow-up project on memory and intelligence after HUNT3 between 2010 and 2011. In 2017, we performed our case-control study using a longitudinal design.

Fig. 1. The study population. AD, Alzheimer's disease; CH, cognitively healthy; FTD, frontotemporal dementia.

examined by a neuropsychologist and categorized as CH [31]. All cases and controls in this study participated in the first study of the North-Trøndelag Health Study (HUNT1) between 1984 and 1986. In the HUNT1 study, participants underwent a brief medical examination and were asked to complete questionnaires including physical and mental health-related items. The HUNT1 study has been described in more detail previously [32].

FTD and AD patients and CH individuals with valid data on smoking habits and obesity were included in our study. Cases and controls with missing data on smoking habits or obesity were excluded.

Dementia Diagnosis

The data on dementia diagnosis in the Hospital Dementia Register were collected retrospectively (1995–2010) and prospectively (2010–2017). The diagnosis was made by specialists in geriatric and psychogeriatric medicine according to national and international guidelines. Diagnoses were based on patient history, caregiver history, clinical examinations, neuropsychological assessments, blood samples, and brain imaging [20, 30].

The Nursing Home Dementia Register consists of data on dementia diagnoses collected from nursing homes in North-Trøndelag in 2010–2011. The data were collected by trained nurses who collected the diagnostic data by conducting tests, measuring cognitive function, neuropsychiatric symptoms, depression symptoms, quality of life, caregiver distress, and personal activities of daily living. Two physicians with wide clinical and research experience independently diagnosed mild cognitive impairment, dementia syndromes, and dementia subtypes. A third expert was consulted if there was any discrepancy [20, 30].

Smoking and Obesity Measurements

Data on smoking and obesity were extracted from the HUNT1 study. The participants in HUNT1 completed self-reporting questionnaires with items on smoking status. The questions were never smoked daily, previously daily smoker, and current daily smoker. In our study, previous daily smoker or daily smoker were categorized as "smoking" and never smoked daily as nonsmoking. The participants in HUNT1 were measured for height and weight (height to the nearest cm, weight to the nearest half kg), and BMI was calculated and documented. We classified patients with a BMI ≥30 as obese.

Confounders

Confounding factors were drawn from the HUNT1 study. We selected variables that might confound the associations between smoking/obesity and FTD/AD. Confounders can

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Table 1. Characteristics of the study population

	FTD	AD	CH
Number of individuals	90	654	116
Female, %	70	69	52.6
Mean age at participation in HUNT1	56.6	60.7	49.1
Mean age at dementia diagnosis	74.4	79.2	
Risk factors present, %			
Heart disease	2.2	4.1	0.9
Diabetes	1.1	0.9	1.7
Hypertension	31.1	37.3	30.2
Smoking	47.8	39.9	46.6
Obesity	14.4	14.7	6.0

AD, Alzheimer's disease; CH, cognitively healthy; FTD, frontotemporal dementia.

influence both the dependent and the independent variable, causing a spurious association. The confounders considered relevant for this study were sex, age at participation in HUNT1, heart disease, diabetes, and hypertension. Heart disease was ascertained if participants indicated that they had experienced angina pectoris or a heart attack. Similarly, diabetes was determined if responses were positive. Hypertension was determined if participants had an average diastolic blood pressure of ≥90 mm Hg.

Statistical Analyses

Datasets from the dementia register of North-Trøndelag Hospital Trust and the HUNT1 study were merged using the personal identification number assigned to all Norwegian citizens. The personal identification number was then replaced with an anonymous project identification number before the merged dataset was made available to the researchers. We evaluated the association between smoking and obesity as measured in HUNT1 and the later development of FTD and AD using multivariable logistic regression. Three analyses were performed independently: (1) analysis of FTD patients versus CH individuals, (2) analysis of FTD patients versus AD patients, and (3) analysis of AD patients versus CH individuals. All of the analyses were performed in four steps: (1) smoking as the only variable, (2) obesity as the only variable, (3) smoking and obesity as the only variables, and (4) smoking and obesity as variables adjusted for the potential confounders of age, sex, heart disease, diabetes, and hypertension. The analyses were performed using SPSS version 25.

Results

Characteristics of the Study Population

The FTD and AD groups were older at participation in HUNT1 and were more likely to have heart disease and hypertension than the CH group. The FTD group had a lower mean age at the time of dementia diagnosis than the AD group, and 14.4% in the FTD group and 14.7% in the AD group had obesity as a risk factor compared to 6.0% in the CH group, while 47.8% in the FTD group and 39.9% in the AD group had smoking as a risk factor compared to 46.6% in the CH group (Table 1).

All cases in the FTD group received their dementia diagnosis after the year 2000. In the AD group, 26 cases received their dementia diagnosis between 1995 and 1999 and the remainder after the year 2000.

Table 2. FTD patients versus CH individuals

	p value	OR	95% CI	
			lower	upper
Smoking[a]	0.218	0.990	0.975	1.006
Obesity[b]	0.049	2.629	1.003	6.894
Smoking[c]	0.302	0.992	0.977	1.007
Obesity[c]	0.064	2.496	0.947	6.582
Adjusted analysis[d]				
Smoking	0.767	0.997	0.980	1.015
Obesity	0.200	2.046	0.685	6.107
Age at participation in HUNT1	0.000	1.106	1.063	1.151
Sex	0.227	0.672	0.352	1.281
Heart disease	0.630	1.834	0.156	21.619
Diabetes	0.664	0.568	0.044	7.315
Hypertension	0.351	0.719	0.359	1.438

Smoking and obesity as risk factors for FTD compared with CH. CH, cognitively healthy; CI, confidence interval; FTD, frontotemporal dementia; OR, odds ratio. [a] Smoking entered as variable. [b] Obesity entered as a variable. [c] Smoking and obesity entered as variables. [d] Smoking, obesity, and confounders entered as variables.

FTD Patients Compared to CH Individuals

In the initial analysis entering only smoking as the variable, no significant association between smoking and FTD development was seen (p = 0.218; odds ratio [OR]: 0.990; 95% confidence interval [CI]: 0.975–1.006) compared with the CH group. When entering only obesity as the variable, a significant association between obesity and FTD development was seen (p = 0.049; OR: 2.629; 95% CI: 1.003–6.894). When both smoking and obesity were entered as variables, a nearly significant increase in the risk of FTD development was observed for obesity (p = 0.064; OR: 2.496; 95% CI: 0.947–6.582). There was no significant association between smoking and the risk of developing FTD (p = 0.302; OR: 0.992; 95% CI: 0.977–1.007). After adjusting for the potential confounders, there were no associations between smoking or obesity and FTD development (Table 2).

FTD Patients Compared to AD Patients

In the initial analysis entering only smoking as the variable, no significant association between smoking and FTD development was seen (p = 0.600; OR: 1.004; 95% CI: 0.990–1.017) compared with the AD group. When entering only obesity as the variable, no significant association between obesity and FTD development was seen (p = 0.953; OR: 0.981; 95% CI: 0.525–6.894) compared with the AD group. When both smoking and obesity were entered as variables, there were no significant associations between smoking and FTD development (p = 0.600; OR: 1.004; 95% CI: 0.990–1.017) or between obesity and FTD development (p = 0.949; OR: 0.980; 95% CI: 0.524–1.833) compared with AD. No significant associations for smoking or obesity were seen after adjusting for potential confounders (Table 3).

AD Patients Compared to CH Individuals

In the initial analysis entering only smoking as the variable, a significant association for developing AD was seen (p = 0.014; OR: 0.987; 95% CI: 0.977–0.997). When entering only obesity as the variable, a significant association for developing AD was also seen (p = 0.015;

Table 3. FTD patients versus AD patients

	p value	OR	95% CI	
			lower	upper
Smoking[a]	0.600	1.004	0.990	1.017
Obesity[b]	0.953	0.981	0.525	6.894
Smoking[c]	0.600	1.004	0.990	1.017
Obesity[c]	0.949	0.980	0.524	1.833
Adjusted analysis[d]				
Smoking	0.789	1.002	0.988	1.015
Obesity	0.658	1.163	0.595	2.274
Age at participation in HUNT1	0.000	0.940	0.915	0.966
Sex	0.522	0.847	0.510	1.407
Heart disease	0.523	0.653	0.176	2.417
Diabetes	0.957	1.062	0.120	9.392
Hypertension	0.305	0.771	0.468	1.268

Smoking and obesity as risk factors for FTD compared with AD. AD, Alzheimer's disease; CI, confidence interval; FTD, frontotemporal dementia; OR, odds ratio. [a] Smoking entered as variable. [b] Obesity entered as a variable. [c] Smoking and obesity entered as variables. [d] Smoking, obesity, and confounders entered as variables.

Table 4. AD patients versus CH individuals

	p value	OR	95% CI	
			lower	upper
Smoking[a]	0.014	0.987	0.977	0.997
Obesity[b]	0.015	2.679	1.211	5.928
Smoking[c]	0.011	0.987	0.976	0.997
Obesity[c]	0.013	2.736	1.233	6.069
Adjusted analysis[d]				
Smoking	0.227	0.992	0.979	1.005
Obesity	0.156	1.954	0.775	4.929
Age at participation in HUNT1	0.000	1.158	1.126	1.191
Sex	0.108	0.678	0.422	1.089
Heart disease	0.525	1.868	0.272	12.831
Diabetes	0.243	0.345	0.058	2.063
Hypertension	0.884	0.963	0.583	1.592

Smoking and obesity as risk factors for AD compared with CH. AD, Alzheimer's disease; CH, cognitively healthy; CI, confidence interval; OR, odds ratio. [a] Smoking entered as a variable. [b] Obesity entered as a variable. [c] Smoking and obesity entered as variables. [d] Smoking, obesity, and confounders entered as variables.

OR: 2.679; 95% CI: 1.211–5.928). When both smoking and obesity were entered as variables, a significant increase in the risk of developing AD was observed both for smoking ($p = 0.011$; OR: 0.987; 95% CI: 0.976–0.997) and obesity ($p = 0.013$; OR: 2.736; 95% CI: 1.233–6.069). The significant associations disappeared after adjusting for potential confounders (smoking: $p = 0.227$; OR: 0.992; 95% CI: 0.979–1.005; obesity: $p = 0.156$; OR: 1.954; 95% CI: 0.775–4.929) (Table 4).

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Discussion

This study investigated the association between smoking and obesity and the risk of developing FTD or AD. When patients with FTD were compared with CH individuals, obesity was more likely to be measured at baseline in HUNT1 among those who later developed FTD.

To the best of our knowledge, no other studies have investigated the associations between obesity and FTD compared with a CH control group. In our earlier study, we used the cases and controls as in the present study, but data on risk factors were collected from the HUNT2 study (1995–1997). The aim of that study was to assess anxiety and depression as risk factors for FTD and AD. Obesity was added as a potential confounder in the adjusted analyses. In the adjusted analyses in that study, a significant association was seen between obesity and FTD compared with CH individuals [20].

When FTD patients were compared with CH individuals in our present study, there were no significant associations between smoking and FTD in the adjusted analyses. This finding is in line with one other study assessing tobacco consumption in FTD outpatients and 151 controls, which found no significant associations for tobacco use [33].

When FTD patients were compared to AD patients, no significant associations were found between obesity or smoking and FTD. To our knowledge, only one other study has assessed smoking as a risk factor for FTD compared with AD. In a study performed by Atkins et al. [34], significant associations were found between obesity and smoking in cases with early-onset FTD compared with a control group of early-onset AD. The individuals with early-onset FTD were more likely to be current smokers (OR: 3.12; 95% CI: 1.04–9.09) and to have a higher body weight (OR: 1.03; 95% CI: 1.01–1.06).

A possible explanation for the differences in the findings between the present study and the study by Atkins et al. [34] may be that the mean age for the onset of dementia in both groups in their study was 56 years, while in our study it was 74.4 years for FTD and 79.2 years for AD. The smoking variable was also grouped into "never," "ex," or "current" in the study of Atkins et al. [34]. In our study, the smoking variable was grouped into "no" (never smoked) or "yes" (current smoker or ex-smoker). Another possibility for the difference is that the FTD population in our study was smaller.

When AD patients were compared with CH individuals, smoking and obesity were more likely to be reported at baseline in HUNT1 among those who later developed AD than in the CH control group. This is in line with findings in other studies, where both smoking and obesity were identified as risk factors for AD [27, 35–37].

Strengths and Limitations of This Study

The main strength of our study is its design. A longitudinal, population-based, nested case-control design allowed us to assess risk factors 15–31 years before diagnosis. Another strength is the use of a validated dementia diagnosis from the dementia register and data on obesity and smoking from HUNT1. In addition, the CH control group consisted of verified CH individuals.

There were limitations to our study regarding some of the dementia diagnoses. Some dementia diagnoses from the Hospital Dementia Register were recorded retrospectively. Most patients were examined by multiple doctors who implemented standard routines, but some files had missing data. This may have reduced the validity of some diagnoses [30].

The dementia diagnoses in the Nursing Home Dementia Register were based on a review of data collected from patients, their family members, and their caregivers. Two physicians with extensive clinical and research experience found the data sufficient to make the dementia diagnosis based on the data [30]. Diagnosing FTD in patients living in nursing homes is more difficult than in those attending hospital outpatient clinics. AD patients often develop

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symptoms and behavior similar to FTD patients late in the course of the disease, which may lead to an incorrect FTD diagnosis [20, 30]. A possible misclassification of dementia type may therefore have affected the findings in our study [20].

Finally, since the data on smoking were self-reported, there is a possibility that the scoring may be biased. Differences in understanding and interpretation of the smoking items may be subject to individual variation. Filling out a self-reported questionnaire may be problematic for individuals with cognitive impairment. It is not likely that FTD or AD cases had developed cognitive impairment before participation in HUNT1, but the possibility cannot be excluded.

Interpretations

One of the findings of our study is that smoking is a risk factor for AD, but not for FTD. Smoking is a well-known risk factor for AD [11, 12] that is thought to be mediated through cardiovascular risk factors [11, 12, 25]. The role of cardiovascular risk factors in FTD has been investigated less [3, 14]. It is possible that cardiovascular risk factors have less of an impact on FTD than on AD.

To the best of our knowledge, our study is the only one that has assessed smoking as a risk factor for FTD, with a span of 15–31 years between measurement of smoking and the time of dementia diagnosis. The findings regarding smoking are interesting and should be further investigated in future studies.

Another important finding in our study was that obesity is a risk factor for both AD and FTD. The findings in our earlier study [20] and in the present study suggest that obesity may be a risk factor for FTD from midlife onwards. Still, it is important to consider whether obesity in FTD may be due to the prodromal phase, as changes in eating habits with preferences of sweets and carbohydrates are a common symptom of FTD [4, 7, 8, 20].

An important consideration for the findings in our study is that we do not have any genetic data on the FTD or AD cases in the population. It is possible that some of the FTD and AD cases developed a dementia disease due to hereditary predisposition.

Conclusion

The findings in our study suggest that smoking is a risk factor for AD, but not FTD. Further, they suggest that obesity is a risk factor for both FTD and AD. The differences and similarities between FTD and AD should be considered in future research, which requires studies with longitudinal designs. Future research on modifiable risk factors for FTD should also separate genetic and sporadic cases of FTD. This would provide a clearer understanding of the roles of modifiable and nonmodifiable risk factors of FTD.

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Statement of Ethics

The study was performed at Namsos Hospital, North-Trøndelag Health Trust, with approval from the Regional Ethics Committee and the Norwegian Ethics Committee. Participating patients gave written consent to take part in the HUNT1 and HUNT3 studies [29, 32].

Disclosure Statement

The authors have no conflicts of interest to declare.

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Appendices

Appendix 1

Informant letter to the participants in Study 2

Appendix 2

Interview guide used in Study 2

Appendix 3

Questionnaires in HUNT1

Appendix 4

Questionnaires in HUNT2

FORESPØRSEL OM DELTAGELSE I ET FORSKNINGSPROSJEKT.

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie for å få mer kunnskap om tidlige symptomer eller sykdomstegn på sykdommen Frontotemporal demens, også kalt Frontallappsdemens. Vanlig forkortelse for denne sykdommen er FTD. Du blir forspurt om å delta i studien fordi du er pårørende til en person som har fått diagnosen FTD. Det er til sammen 15 forespurte som blir valgt ut til å delta i studien. Ansvarlige for dette prosjektet er Helse Nord-Trøndelag og Norges teknisk-naturvitenskapelige universitet, NTNU. Prosjektleder er psykiatrisk sykepleier og doktorgradsstipendiat Hege Rasmussen, Sykehuset Namsos.

Hva innebærer studien?
Studien innebærer at Hege Rasmussen intervjuer deg i 45-60 minutter. Spørsmålene i intervjuet vil dreie seg om hvordan du opplevde tidlige symptomer eller tegn på endringer hos personen som har fått diagnosen FTD. Intervjuet blir tatt opp på lydbånd og i løpet av noen dager blir intervjuet skrevet ned som tekst. Det er kun Hege Rasmussen som har tilgang til lydbåndet av opptaket og tekstmaterialet. Det er til sammen 15 personer som skal intervjues på samme måte som deg. Tekstmaterialet fra alle disse intervjuene skal analyseres vitenskapelig og publiseres som en forskningsartikkel.

Mulige fordeler og ulemper
Deltagelse innebærer at du må møte opp til intervju på avdelingen der personen ble utredet og fikk diagnosen FTD. Dersom dette medfører lang reisevei for deg, kan Hege Rasmussen undersøke muligheter for å finne et møtested nærmere der du bor. Det kan hende at du vil synes at det er belastende eller ubehagelig å bli intervjuet om temaet som gjelder. Du kan når som helst avbryte intervjuet uten å gi noen nærmere forklaring om dette.

Hva skjer med informasjonen du gir i intervjuet?
Intervjuet av deg og informasjonen som registreres skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det betyr av opplysningene er avidentifisert. Samtykkeskjema og navneliste oppbevares innelåst. Det er kun prosjektleder Hege Rasmussen som har adgang til samtykkeskjema og navnelisten og som kan finne tilbake til deg. Informasjonen som er samlet inn vil slettet fem år etter at intervjuet med deg fant sted, i 2020. Det vil ikke være mulig å identifisere deg eller personen som har FTD i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Du kan avslutte intervjuet når som helst. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side og legger den i den ferdig frankerte konvolutten. Du kan poste den selv, eller be om at en av de ansatte på avdelingen hvor du fikk utdelt informasjonsskrivet poster det for deg. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke når som helst uten at det vil bli stilt noen spørsmål rundt dette. På samtykkeerklæringen bes du også om å oppgi ditt telefon nummer. Etter at Hege Rasmussen har mottatt samtykkeerklæringen fra deg, vil hun ta kontakt med deg på telefon for å avtale møte for intervju.

Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Hege Rasmussen tlf:**480 45 909.**

Ytterligere informasjon om studien finnes i kapittel A.

Ytterligere informasjon om personvern finnes i kapittel B.

Samtykkeerklæring følger etter kapittel B.

Kapittel A- utdypende forklaring av hva studien innebærer.

Kriterier for å delta i studien:
Kriteriene for å delta som informant i studien er at du har bodd sammen med en person som har fått sykdommen Frontotemporaldemens i minst to år.

Bakgrunnsinformasjon om studien:
Frontotemporaldemens (FTD) er en av de vanligste demensdiagnosene med tidlig debut. Kunnskapen om tidlige symptomer, årsaker og risikofaktorer for FTD er ufullstendig i internasjonal litteratur. Det er logisk å tenke at det er nærmeste pårørende som først merker tegn til endring hos den FTD rammende. Det foreligger lite forskning på hva de tidlige endringer går ut på, hvor tidlig de inntreffer og hvordan pårørende opplever dem. Primærhelsetjeneste og spesialhelsetjeneste har behov for mer kunnskap om tidlige tegn til sykdommen for å stille riktig diagnose på et tidligere stadium.

Kapittel B- Personvern.
Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det betyr av opplysningene er avidentifisert. I intervjuet blir det lagt vekt på dine opplevelser og beskrivelser av tidlige tegn på sykdom hos personen som har FTD. Det er disse opplysningene som er viktige for undersøkelsen. Det vil ikke være mulig på noen måte identifisere personen som har FTD i forskningsartikkelen som skal skrives.

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

Informasjon om utfallet av studien.
Du har rett til å få informasjon om utfallet/resultatet av studien. Du vil få tilbud om å få lese artikkelen som blir utarbeidet etter intervjuene.

[Skriv her] [Skriv her] **Appendix 1**

SAMTYKKE TIL DELTAGELSE I STUDIEN:

Jeg er villig til å delta i studien.
Jeg ønsker at Hege Rasmussen tar kontakt på telefon:……..

(Signering: Av informanten, dato.)
……..

Jeg bekrefter å ha gitt informasjon om studien.

(Signering, prosjektleder Hege Rasmussen, dato)
……

Intervjuguide studie 2.

- Kan du fortelle om den første gangen du opplevde at samboeren din/ektefellen hadde endret seg?

  - Hva betydde endringene for deg?
  - Hva gikk endringene ut på?
  - Hvordan opplevde du endringene?
  - Hva innebar disse opplevelsene for deg?

MELDING OM SKJERMBILDEFOTOGRAFERING OG UNDERSØKELSE AV BLODTRYKK OG BLODSUKKER

Skjermbildefotograferingen kommer nå til ditt distrikt. Denne gangen inngår fotograferingen i en større helseundersøkelse, og vi viser til orienteringen som er gitt i den vedlagte brosjyre.

Tid og sted for frammøte vil du finne nedenfor.

Vennligst fyll ut spørreskjemaet på baksiden og ta det med til undersøkelsen. Ta også med skjermbildebevis, tuberkulinkort eller helsebok om du har.

Det er viktig at du møter fram selv om du nylig har fått kontrollert blodtrykk eller blodsukker, og selv om du er under behandling for høyt blodtrykk eller for sukkersyke.

Med vennlig hilsen

Statens skjermbildefotografering

Postboks 8155 Dep, Oslo 1

Fylkeslegen • Helserådet • Statens Institutt For Folkehelse

Født dato | Personnr. | Kommune | Kretsnr.

Møtested | Kjønn | Første bokstav etternavn | Dag og dato | Klokkeslett

H. 14 | V. 18 | SBT_1 21 | DBT_1 24 | PULS 27 | SBT_2 30 | DBT_2 33 | SYKEPL 36

TID 38 | GLUC 39 | GLUC 42 | GLUC 45 | HG 46 | RT 47 | P 48 | ØM 49

Vi takker for frammøtet til undersøkelsen.

Vi vil også be deg være vennlig å fylle ut dette spørreskjemaet. Opplysninger vil bli brukt i et større forskningsarbeid om forhold som har betydning for helsen.

Svar etter beste skjønn. Kryss av for bare en av svar-mulighetene (dersom det ikke står nevnt noe annet). Det utfylte skjema returneres i vedlagte svarkonvolutt. Porto er betalt.

Alle opplysningene er underlagt streng taushetsplikt.

Med hilsen

Statens skjermbildefotografering
Fylkeslegen ● Helserådet ● Statens Institutt For Folkehelse
Institutt for anvendt samfunnsvitenskapelig forskning/
Institutt for samfunnsforskning

Til etikett

Navn: _____

Adr.: _____

_____

_____
Postnr. Postkontor

F.nr.: _____

MOSJON

Med mosjon mener vi at du f.eks. går tur, går på ski, svømmer eller driver trening/idrett.

Hvor ofte driver du mosjon?
(Ta et gjennomsnitt)

Aldri	12	1
Sjeldnere enn en gang i uka		2
En gang i uka		3
2–3 ganger i uka		4
Omtrent hver dag		5

Dersom du driver slik mosjon så ofte som en eller flere ganger i uka:
Hvor hardt mosjonerer du?
(Ta et gjennomsnitt)

Tar det rolig uten å bli andpusten eller svett	13	1
Tar det så hardt at jeg blir andpusten og svett		2
Tar meg nesten helt ut		3

Hvor lenge holder du på hver gang?
(Ta et gjennomsnitt)

Mindre enn 15 minutter	14	1
16–30 minutter		2
30 minutter–1 time		3
Mer enn 1 time		4

SALT

Hvor ofte bruker du salt kjøtt eller salt fisk/sild til middag?

Aldri, eller sjeldnere enn en gang i måneden	15	1
1–2 ganger i måneden		2
Opptil en gang i uka		3
Opptil to ganger i uka		4
Mer enn to ganger i uka		5

Hvor ofte pleier du å strø ekstra salt på middagsmaten?

Sjelden eller aldri	16	1
Av og til		2
Ofte		3
Alltid eller nesten alltid		4

RØYKEVANER

		JA	NEI
Røyker du daglig for tiden?	17		
Hvis du svarte «JA», røyker du DAGLIG for tiden:		JA	NEI
Sigaretter?	18		
Pipe?	19		
Sigarer (eller serutter/sigarillos)?	20		
Hvis du IKKE røyker SIGARETTER daglig for tiden: Har du røykt SIGARETTER daglig tidligere?	21	JA	NEI

Hvis du svarte «JA», hvor lenge er det siden du sluttet å røyke sigaretter daglig?

Mindre enn 3 måneder	22	1
3 måneder– 1 år		2
1–5 år		3
Mer enn 5 år		4

Hvis du røyker SIGARETTER daglig nå, eller har gjort det tidligere:

		Antall
Hvor mange sigaretter røyker eller røykte du pr. dag? (Oppgi antall pr. dag medregnet håndrullede)	23	

Besvares av dem som røyker daglig nå eller har røykt daglig tidligere:
(Gjelder både sigarett-, pipe- og sigar-røykere)

Hvor gammel var du da du begynte å røyke daglig?	25	år
Hvor mange år tilsammen har du røykt daglig?	27	år

ALKOHOLBRUK

Hvor ofte har du drukket alkohol (øl, vin eller brennevin) de SISTE 14 DAGENE?

Jeg har ikke drukket alkohol, men er ikke totalavholdende	29	1
Jeg har drukket 1–4 ganger		2
Jeg har drukket 5–10 ganger		3
Jeg har drukket mer enn 10 ganger		4
Jeg er totalavholdende, drikker aldri alkohol		5

		JA	NEI
Dersom du har drukket alkohol de siste 14 dagene, har det ført til at du noen gang har følt deg beruset?	30		

Har det vært perioder i livet ditt da du har drukket for mye, eller i hvert fall i meste laget?

Nei	31	1
I tvil, kanskje		2
Ja		3

A. Hvordan er helsa di for tida?
(Sett kryss i bare *en* rute.)

Dårlig	50	1
Ikke helt god		2
God		3
Svært god		4

B. Har du i løpet av de siste 12 måneder vært hos?

	JA	NEI
Almenpraktiserende lege (distriktslege, privatpraktiserende lege,turnuskandidat) 51		
Bedriftslege 52		
Militærlege 53		
Lege ved sykehus (uten at du var innlagt) 54		
Annen lege 55		

C. Har du vært innlagt i sykehus de siste 5 åra? 56 | JA | NEI |

D. Bruker du, eller har du brukt, medisin for høyt blodtrykk? 57 | JA | NEI |

E. Har du eller har du hatt noen av disse sykdommene?

	JA	NEI
Sukkersyke 58		
Hjerteinfarkt 59		
Angina pectoris (hjertekrampe) 60		
Hjerneslag eller hjerneblødning 61		

F. Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? (Med langvarig menes at det har vart, eller vil vare i minst ett år.) 62 | JA | NEI |

Hvis «JA», vil du si at dine funksjoner er litt, middels eller mye nedsatt?

	LITT	MIDDELS	MYE
Er bevegelseshemmet 63			
Har nedsatt syn 64			
Har nedsatt hørsel 65			
Hemmet pga. kroppslig sykdom 66			
Hemmet pga. psykiske plager 67			

G. Har du noen søsken? (Nålevende eller døde) 68 | JA | NEI |

Hvis «JA», har en eller flere av dem hatt noen av disse sykdommene?

	JA	NEI	VET IKKE
Sukkersyke 69			
Hjerteinfarkt/hjertekrampe 70			
Forhøyet blodtrykk 71			

H. Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen, eller er du stort sett misfornøyd?
(Sett kryss i bare *en* rute.)

Svært fornøyd 72		1
Meget fornøyd		2
Ganske fornøyd		3
Både/og		4
Nokså misfornøyd		5
Meget misfornøyd		6
Svært misfornøyd		7

SELVE BLODTRYKKSMÅLINGEN I DEN VEDLAGTE BROSJYREN

	JA	NEI	VET IKKE

I. Er blodtrykket ditt målt noen gang før? 73
Hvis «NEI», gå videre til spørsmål M

J. Hvilket år ble blodtrykket målt siste gang?

19 ☐☐ vet ikke 74

Skriv årstallet her (ca.)

K. Hvor ble blodtrykket målt siste gang?
(Sett kryss i bare *en* rute.)

Hos almenpraktiserende lege (distriktslege, privatpraktiserende lege, turnuskandidat 76		1
Hos bedriftslege		2
Hos militærlege		3
På sykehus		4
Hos annen lege		5
Vet ikke		6

L. Hva ble resultatet av målingen?
(Sett kryss i bare *en* rute.)

Jeg skulle begynne med eller fortsette med medisin for høyt blodtrykk 77		1
Jeg skulle komme til kontroll, men skulle *ikke* ta medisin		2
Jeg skulle *ikke* ta medisin og *ikke* komme til kontroll		3

M. Dersom denne helseundersøkelsen viser at du bør undersøkes nærmere: Hvilken almenpraktiserende lege ønsker du da å bli henvist til?

Skriv navnet på legen her

IKKE SKRIV HER

Ingen spesiell lege 78

OM ARBEIDET DITT

N. Er du i arbeid for tida?
(Sett kryss i bare *en* rute.)

Ja, heltidsarbeid (utenom husarbeid) 81		1
Ja, deltidsarbeid (utenom husarbeid)		2
Ja, heltids husarbeid		3
Nei, ikke i arbeid		4

O. Hvis du ikke er i heltids arbeid, er det på grunn av:
(Sett kryss i bare *en* rute.)

Arbeidsløshet, permittering 82		1
Pensjon eller trygd		2
Utdanning eller militærtjeneste		3
Annet		4

HVIS DU ER I ARBEID AVENNLIGST SVAR PÅ DE NESTE TO SPØRSMÅLENE:

P. Er det mye stress og mas på arbeidet ditt?
(Sett kryss i bare *en* rute.)

Nei, ikke i det hele tatt 83		1
Sjelden		2
Ja, en god del		3
Ja, nesten hele tida		4

Q. Kan du sjøl bestemme hvordan arbeidet ditt skal legges opp? (Sett kryss i bare *en* rute)

Nei, ikke i det hele tatt 84		1
I liten grad		2
Ja, stort sett		3
Ja, det bestemmer jeg sjøl		4

Spørreskjemaet er en viktig del av Helseundersøkelsen. Her finner du spørsmål om tidligere sykdom og om andre forhold som har betydning for helsa. Vennligst fyll ut skjemaet på forhånd og ta det med til Helseundersøkelsen. Dersom enkelte spørsmål er uklare, lar du dem bare stå ubesvarte til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen. Alle svar vil bli behandlet strengt fortrolig.

Flere steder i skjemaet ber vi deg oppgi din alder da eventuell sykdom inntrådte. Hvis du ikke husker nøyaktig hvor gammel du var, skriver du et tall som er nærmest det du antar er korrekt.

Når resultatene fra undersøkelsen foreligger, vil det være enkelte som trenger ny undersøkelse hos egen lege. Dette vil du få beskjed om i det brevet som vi sender deg om dine resultater. Samtidig sender vi melding om resultatene dine til legen din. Det er derfor om å gjøre at du i rubrikken helt til slutt i skjemaet oppgir navnet på den allmennpraktiserende lege, kommunelege eller det helsesenter som du ønsker skal ta hånd om eventuell etterundersøkelse, og som vi skal sende resultatene til.

Med vennlig hilsen

Helsetjenesten i Nord-Trøndelag • Statens helseundersøkelser • Statens Institutt for Folkehelse

DET HANDLER OM HELSA DI

Hvordan er helsa di nå?
Bare ett kryss

Dårlig	12	☐ 1
Ikke helt god		☐ 2
God		☐ 3
Svært god		☐ 4

LUFTVEGSPLAGER

	JA	NEI	
Hoster du daglig i perioder av året?			
Hvis JA:			
Er hosten vanligvis ledsaget av oppspytt?	14		
Har du hatt hoste med oppspytt i minst 3 mnd. sammenhengende i hvert av de to siste åra?			
Har du hatt noe anfall med pipende eller tung pust de siste 12 måneder?	16		

	JA	NEI	Alder første gang	
Har du eller har du hatt astma?	17			år

	JA	NEI	
Har du brukt eller bruker du astmamedisiner?	20		

HJERTE-KARSYKDOMMER, DIABETES

Har du, eller har du hatt:	JA	NEI	Alder første gang
Hjerteinfarkt	21		år
Angina pectoris (hjertekrampe)	24		år
Hjerneslag/hjerneblødning	27		år
Diabetes (sukkersyke)	30		år

Hva ble resultatet siste gang du målte blodtrykket ditt?
Bare ett kryss

Begynne med/fortsette med blodtrykksmedisin	33	☐ 1
Komme til kontroll, men ikke ta blodtrykksmedisin		☐ 2
Ingen kontroll og ingen medisin nødvendig		☐ 3
Har aldri fått målt blodtrykket		☐ 4

Bruker du medisin mot høyt blodtrykk?
Bare ett kryss

Nå	34	☐ 1
Før, men ikke nå		☐ 2
Aldri brukt		☐ 3

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?			

STOFFSKIFTE

Har du noen gang fått påvist:	JA	NEI	Alder første gang	
for høyt stoffskifte	36			år
for lavt stoffskifte	39			år
struma	42			år
annen sykdom i skjoldbruskkjertelen				år
Bruker du eller har du brukt noen av disse medisinene:				
Thyroxin	48			år
Neo-Mercazole	51			år
Er du operert i skjoldbruskkjertelen				år
Har du fått radiojodbehandling	57			år

MUSKEL/SKJELETT-PLAGER

	JA	NEI	
Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?	60		

Hvis NEI, gå videre til neste side øverst.
Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?

		JA	NEI
Nakke	61		
Skuldre (aksler)			
Albuer			
Håndledd, hender			
Bryst/mage	65		
Øvre del av ryggen			
Korsryggen			
Hofter			
Knær			
Ankler, føtter	70		

Hvis du har hatt plager i flere områder i minst 3 mnd. det siste året, setter du ring rundt det ja-krysset hvor plagene har vart lengst

Hvor lenge har plagene vart sammenhengende?
Svar for det området hvor plagene har vart lengst

Hvis under 1 år, oppgi antall mnd.	71
Hvis 1 år eller mer, oppgi antall år.	73

Antall mnd.

Antall år

Har plagene redusert din arbeidsevne det siste året?
Gjelder også hjemmearbeidende. Bare ett kryss

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐	☐	☐	☐

	JA	NEI	IKKE I ARBEID	
Har du vært sykmeldt pga. disse plagene det siste året?	76			

	JA	NEI
Har plagene ført til redusert aktivitet i fritida?		

Har lege noen gang sagt at du har/har hatt noen av disse sykdommene:

	JA	NEI
Beinskjørhet (osteoporose) 78		
Fibromyalgi (fibrositt/kronisk smertesyndrom)		
Leddgikt (reumatoid artritt)		
Slitasjegikt (artrose)		
Bechterews sykdom 82		
Andre langvarige skjelett- eller muskelsykdommer		

Har du noen gang hatt:

	JA	NEI	Alder siste gang
Lårhalsbrudd 84			år
Brudd i håndledd/underarm 87			år
Nakkesleng (whiplash) 90			år
Skade som førte til sykehusinnleggelse			år

ANDRE PLAGER

I hvilken grad har du hatt disse plagene i de siste 12 månedene?

	Ikke plaget	Litt plaget	Mye plaget
Kvalme 96			
Brystbrann/sure oppstøt			
Diaré			
Treg mage			
Hjertebank			
Åndenød 101			

ANDRE SYKDOMMER

Har du eller har du noen gang hatt:

	JA	NEI	Alder første gang
Epilepsi 102			år
Psykiske plager hvor du har søkt hjelp			år
Kreftsykdom 108			år
Annen langvarig sykdom 111			

DAGLIGE FUNKSJONER

Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? 112 — JA / NEI

Langvarig: minst ett år

Hvis JA:

Hvor mye vil du si at dine funksjoner er nedsatt?

	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet 113			
Har nedsatt syn			
Har nedsatt hørsel			
Hemmet pga. kroppslig sykdom.			
Hemmet pga. psykiske plager... 117			

MENN fortsetter øverst neste spalte

BESVARES BARE AV KVINNER

Hvor mange barn har du født? 118 — Antall barn

Sett 0 hvis du ikke har født barn

Hvis du har født barn, besvar:

Hvor gammel var du da du fødte ditt første barn? 120 — Alder: ___ år

Hvor gammel var du da du fødte ditt siste barn? 122 — ___ år

Besvares ikke hvis du har født bare ett barn

Hvor gammel var du da du fikk menstruasjon? 124 — ___ år

Sett 0 hvis du ikke noen gang har hatt menstruasjon

Fortsett neste spalte øverst

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? 126 — JA / NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? 127 — JA / NEI

Hvor lenge er du vanligvis daglig til stede i røykfylt rom? 128 — Antall timer

Sett 0 hvis du ikke oppholder deg i røykfylt rom

Røyker du selv?

	JA	NEI
Sigaretter daglig? 130		
Sigarer/sigarillos daglig?		
Pipe daglig? 132		

Aldri røykt daglig *(Sett kryss)* ☐

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? 134 — Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? 136 — Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig? 140 — Alder: ___ år

Hvor mange år tilsammen har du røykt daglig? 142 — Antall år

KAFFE/TE/ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?

Sett 0 hvis du ikke drikker kaffe/te daglig

	Antall kopper
Kokekaffe 144	
Annen kaffe 146	
Te 148	

Alkohol:
Er du total avholdsmann/-kvinne? 150 — JA / NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? 151 — Antall ganger

Regn ikke med lettøl. Sett 0 hvis mindre enn 1 gang i mnd.

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker?

Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol 153

Øl	Vin	Brennevin
glass	glass	glass

FYSISK AKTIVITET

I FRITIDA

Hvordan har din fysiske aktivitet i fritida vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*

Arbeidsveg regnes som fritid

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)* 159	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)* 160	☐ 1	☐ 2	☐ 3	☐ 4

UNDER ARBEID

Hvis du er i lønnet eller ulønnet arbeid:

Hvorledes vil du beskrive arbeidet ditt?

Bare ett kryss

For det meste stillesittende arbeid *(f.eks. skrivebordsarbeid, montering)* 161 ☐ 1

Arbeid som krever at du går mye *(f.eks. ekspeditørarb., lett industriarb., undervisning)* ☐ 2

Arbeid hvor du går og løfter mye *(f.eks. postbud, pleier, bygningsarbeid)* ☐ 3

Tungt kroppsarbeid *(f.eks. skogsarbeid, tungt jordbruksarb.,tungt bygningsarb.)* ☐ 4

Bla om!

HVORLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Trygg og rolig? 162	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Har du følt deg:				
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst? 165	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom? 168	☐ 1	☐ 2	☐ 3	☐ 4

Her kommer noen flere spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uka. Ikke tenk for lenge på svaret - de spontane svarene er best

Jeg gleder meg fortsatt over ting slik jeg pleide før 169
Avgjort like mye ..... ☐ 1 Bare lite grann ..... ☐ 3
Ikke fullt så mye ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har en urofølelse som om noe forferdelig vil skje 170
Ja, og noe svært ille .... ☐ 1 Litt, bekymrer meg lite . ☐ 3
Ja, ikke så veldig ille ... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan le og se det morsomme i situasjoner 171
Like mye nå som før .... ☐ 1 Avgjort ikke som før .... ☐ 3
Ikke like mye nå som før ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har hodet fullt av bekymringer 172
Veldig ofte ..... ☐ 1 Av og til ..... ☐ 3
Ganske ofte ..... ☐ 2 En gang i blant ..... ☐ 4

Jeg er i godt humør 173
Aldri ..... ☐ 1 Ganske ofte ..... ☐ 3
Noen ganger ..... ☐ 2 For det meste ..... ☐ 4

Jeg kan sitte i fred og ro og kjenne meg avslappet 174
Ja, helt klart ..... ☐ 1 Ikke så ofte ..... ☐ 3
Vanligvis ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg som om alt går langsommere 175
Nesten hele tiden ..... ☐ 1 Fra tid til annen ..... ☐ 3
Svært ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg urolig som om jeg har sommerfugler i magen 176
Ikke i det hele tatt ..... ☐ 1 Ganske ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært ofte ..... ☐ 4

Jeg bryr meg ikke lenger om hvordan jeg ser ut 177
Ja, har sluttet å bry meg ☐ 1 Kan hende ikke nok .... ☐ 3
Ikke som jeg burde ..... ☐ 2 Bryr meg som før ..... ☐ 4

Jeg er rastløs som om jeg stadig må være aktiv 178
Uten tvil svært mye ..... ☐ 1 Ikke så veldig mye ..... ☐ 3
Ganske mye ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg ser med glede frem til hendelser og ting 179
Like mye som før ..... ☐ 1 Avgjort mindre enn før . ☐ 3
Heller mindre enn før ... ☐ 2 Nesten ikke i det hele tatt ☐ 4

Jeg kan plutselig få en følelse av panikk 180
Uten tvil svært ofte ..... ☐ 1 Ikke så veldig ofte ..... ☐ 3
Ganske ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan glede meg over gode bøker, radio og TV 181
Ofte ..... ☐ 1 Ikke så ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært sjelden ..... ☐ 4

UTDANNING

Hvilken utdanning er den høyeste du har fullført?

Grunnskole 7-10 år, framhaldsskole, folkehøgskole ..... 182 ☐ 1
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole ..... ☐ 2
Artium, øk.gymnas, allmennfaglig retning i videregående skole ..... ☐ 3
Høgskole/universitet, mindre enn 4 år ..... ☐ 4
Høgskole/universitet, 4 år eller mer ..... ☐ 5

ARBEID

Hva slags arbeidssituasjon har du nå?
Ett eller flere kryss

Lønnet arbeid ..... 183 ☐
Selvstendig næringsdrivende ..... ☐
Heltids husarbeid ..... ☐
Utdanning, militærtjeneste ..... ☐
Arbeidsledig, permittert ..... ☐
Pensjonist/trygdet ..... 188 ☐

Hvor mange timer lønnet arbeid har du i uka? ..... 189 Antall timer

Har du skiftarbeid, nattarbeid eller går vakt? JA ☐ NEI ☐

ALT I ALT

Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
Bare ett kryss

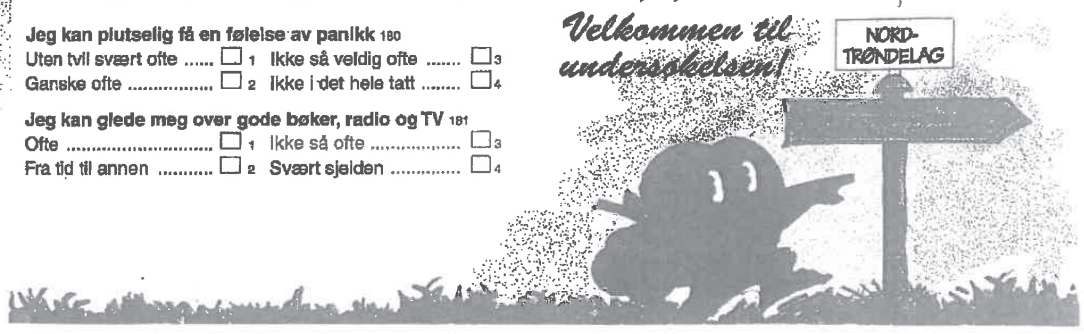
Svært fornøyd ..... 192 ☐ 1
Meget fornøyd ..... ☐ 2
Ganske fornøyd ..... ☐ 3
Både/og ..... ☐ 4
Nokså misfornøyd ..... ☐ 5
Meget misfornøyd ..... ☐ 6
Svært misfornøyd ..... ☐ 7

DIN LEGE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker du skal foreta undersøkelsen?
Skriv navnet på legen her: 193 *Ikke skriv her*

Takk for utfyllingen!

Nok en gang:
Velkommen til undersøkelsen!



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DER DU BOR

Svar ut fra nærmiljøet, dvs. nabolaget/grenda:
Ett kryss for hvert spørsmål

Jeg føler et sterkt fellesskap med de som bor her 86
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

Selv om noen tar initiativ, er det ingen som blir med på det som settes i gang her 87
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Hvis jeg flytter herfra, vil jeg lengte tilbake 88
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Man kan ikke stole på hverandre her 89
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Når noe skal gjøres her, er det lett å få folk med 90
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er vanskelig å få kontakt med folk her 91
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er godt samhold her 92
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Ingen orker å ta initiativ til noe lenger her 93
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk trives godt her 94
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk her kan ha store problemer uten at naboen vet noe 95
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er alltid noen som tar initiativ til å løse nødvendige oppgaver her 96
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk snakker lite med hverandre her 97
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene. Kryss av for "ingen" hvis ingen av slektningene har hatt denne sykdommen: *Evt. flere kryss på hver linje*

	Mor	Far	Bror	Søster	Barn	Ingen
Hjerneslag eller hjerneblødning 98	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder 104	☐	☐	☐	☐	☐	☐
Astma 110	☐	☐	☐	☐	☐	☐
Allergi 116	☐	☐	☐	☐	☐	☐
Kreftsykdom 122	☐	☐	☐	☐	☐	☐
Høyt blodtrykk 128	☐	☐	☐	☐	☐	☐
Psykiske plager 134	☐	☐	☐	☐	☐	☐
Osteoporose (benskjørhet) 140	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke) 146	☐	☐	☐	☐	☐	☐
Alder da de fikk diabetes 152	år	år	år	år	år	

Har du *selv* høysnue eller neseallergi? 162 Ja ☐ Nei ☐

BRUK AV HELSETJENESTER

Har du i løpet av de siste 12 månedene vært hos:
Ett kryss på hver linje

	Ja	Nei
allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat) 169	☐	☐
bedriftslege	☐	☐
lege ved sykehus (uten at du var innlagt)	☐	☐
annen lege	☐	☐
fysioterapeut	☐	☐
kiropraktor	☐	☐
homøopat 169	☐	☐
annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, "healer", "synsk", e.l.)	☐	☐

	Ja	Nei
Har du vært innlagt i sykehus de siste 5 åra? 171	☐	☐

ALKOHOL

Hvis du er totalavholdskvinne: Gå til KOSTHOLD.

Ett kryss for hver spørsmål

	Ja	Nei
Har du noen gang følt at du burde redusere alkoholforbruket ditt? 172	☐	☐
Har andre noen gang kritisert alkoholbruken din? 173	☐	☐
Har du noen gang følt ubehag eller skyldfølelse pga. alkoholbruken din? 174	☐	☐
Har det å ta en drink noen gang vært det første du har gjort om morgenen for å roe nervene, kurere bakrus eller som en oppkvikker? 175	☐	☐

KOSTHOLD

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)? 178 — Antall: ☐

Hvor mange dager i uka spiser du varm middag? ☐

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis? *Inntil to kryss*

Brødtypen ligner mest på 176	Loff	Fint brød	Knepp-brød	Grov-brød	Knekke-brød
	☐	☐	☐	☐	☐

Hva slags *fett* blir vanligvis brukt i din husholdning?
Ett kryss for matlaging og ett kryss for brød

	Til matlaging	På brød
Bruker *ikke* smør eller margarin	183 ☐ 1	184 ☐ 1
Meierismør	☐ 2	☐ 2
Hard margarin	☐ 3	☐ 3
Bløt (sott) margarin	☐ 4	☐ 4
Smør/margarin blanding	☐ 5	☐ 5
Lettmargarin	☐ 6	☐ 6
Oljer	☐ 7	

MEDISINBRUK

	Ja	Nei
Har du i deler av de siste 12 måneder brukt noen medisiner daglig eller nesten daglig? 185	☐	☐

Hvis «Ja»:
Angi hvor mange måneder du brukte følgende medisiner: *Sett 0 hvis du ikke har brukt medisinene*

	Antall mndr.		Antall mndr.
smertestillende 186		hjertemedisin (ikke blodtrykksmedisin)	
sovemedisin 188		annen medisin	
beroligende medisin		*Kosttilskudd:*	
medisin mot depresjon		jerntabletter 202	
allergimedisin 194		vitamintilskudd	
astmamedisin 198		tran/fiskeolje 206	

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden? 200
Daglig ☐ 1 Sjeldnere enn hver uke ☐ 3
Hver uke, men ikke hver dag ☐ 2 Aldri ☐ 4