

Cognitive function and mild cognitive impairment in a general population: roles of cardiovascular and genetic risk factors and magnetic resonance volumetry. The Tromsø Study

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A dissertation for the degree of Philosophiae Doctor – December 2018

ISM skriftserie nr. 197

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Acknowledgements

First and foremost, this thesis would not have seen the light of day without the funding of the Northern Norway Regional Health Authority, the Odd Berg Group Medical Research Fund, the National Association for Public Health and the Norwegian Research Council.

I have received lots of assistance on my Odyssey. Primarily from my main supervisor, Professor Henrik Schirmer, who never lost faith in me. He took the initiative for, and planned the research project that has led to this thesis. His support and advice, also in bleak times, is highly appreciated.

Secondly, I am indebted to my co-supervisor Dr. Elena Kamycheva. This thesis would not have come to fruition without her grit and enterprise. She gave lots of support and granted me a leave of absence to complete the thesis.

Thanks to the department of radiology, University Hospital of North Norway, for good collaboration in the Tromsø Dementia Study.

Thanks to Petter Eldevik, former head of the radiological department, for letting MRI become a part of the Tromsø Dementia Study.

Thanks to Torgil Vangberg for implementing fully automated volumetry with NeuroQuant as part of the Tromsø Dementia Study.

Thanks to the section of nephrology, division of internal medicine at the University Hospital of North Norway, for good collaboration in the second paper on albuminuria and carotid atherosclerosis as predictors of cognitive function.

Thanks to the department of Neurology and Neurophysiology, University Hospital of North Norway, for good collaboration in the second paper on albuminuria and carotid atherosclerosis as predictors of cognitive function.

Thanks to Professor Ellisiv Mathiesen for sound advice and thorough assessment of all papers.

Thanks to Kristin Voie, research nurse in the Tromsø Dementia Study who helped plan the conduct of the study and had a central role in administering it.

Thanks to Inger Sperstad who created the software for cognitive testing, collateral information and interviews in the Tromsø Dementia Study.

Thanks to Professor Tom Wilsgaard for assistance on statistical issues.

Thanks to Rod Wolstenholme for making the figures in all papers.

Thanks to all co-authors, Torgil Vangberg, Petter Eldevik, Gry Wikran, Ellisiv Mathiesen, Henrik Schirmer, Marit D. Solbu, Kjell Arne Arntzen and Marit Herder for their invaluable help.

Lastly, thanks to all the participants and their companions who took part in the Tromsø Dementia Study. They were all agreeable, despite spending much time on the study without compensation.

List of papers

- I Sigbjørn Rogne, Torgil Vangberg, Petter Eldevik, Gry Wikran, Ellisiv B. Mathiesen, Henrik Schirmer. Mild Cognitive Impairment, Risk factors and Magnetic Resonance Volumetry: Role of Probable Alzheimer's Disease in the Family.
Dementia and Geriatric Cognitive Disorders 2013;36:87-98
- II Sigbjørn O. Rogne, Marit D. Solbu, Kjell Arne Arntzen, Marit Herder, Ellisiv B. Mathiesen, Henrik Schirmer. Albuminuria and Carotid Atherosclerosis as Predictors of Cognitive Function in a General Population.
European Neurology 2013;70:340-348
- III Sigbjørn Rogne, Torgil Vangberg, Petter Eldevik, Gry Wikran, Ellisiv B. Mathiesen, Henrik Schirmer. Magnetic Resonance Volumetry: Prediction of Subjective Memory Complaints and MCI, and Associations with Genetic and Cardiovascular Risk Factors.
Dementia and Geriatric Cognitive Disorders EXTRA 2016;6:529-540

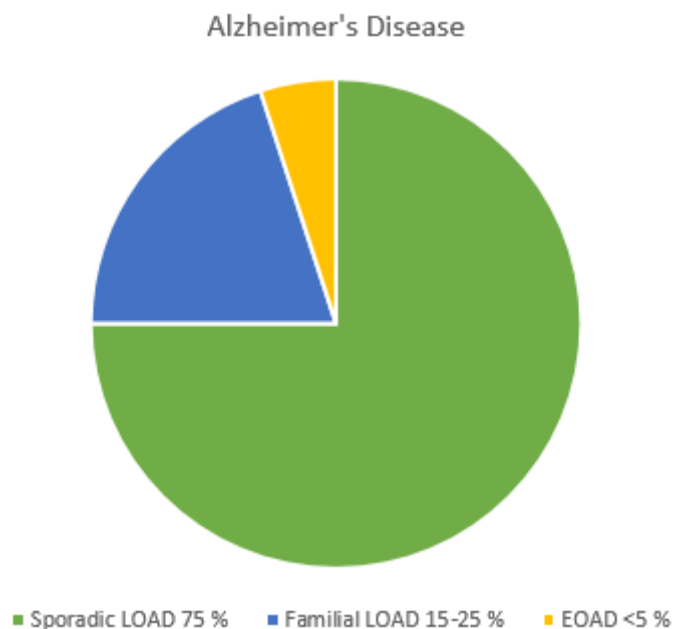
Abbreviations

A β	Amyloid beta
ACR	Urinary albumin-creatinine ratio
AD	Alzheimer's disease
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
CSF	Cerebrospinal fluid
CSVD	Cerebral small vessel disease
CT	Computed tomography
DLBD	Dementia of Lewy bodies
DST	Digit-symbol coding test
eGFR	Estimated glomerular filtration rate
EOAD	Early-onset Alzheimer's disease
FLD	Frontotemporal dementia
FTT	Finger-tapping test
Hcy	Homocysteine
IMT	Right internal carotid artery intima media thickness
LOAD	Late-onset Alzheimer's disease
MCI	Mild cognitive impairment
MMSE	Mini mental status examination
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangle
p-tau	Phosphorylated tau protein
PET	Positron emission tomography
SMC	Subjective memory complaints
tHcy	Total plasma homocysteine
t-tau	Total tau protein
TPA	Right internal carotid artery total plaque area
VaD	Vascular dementia
VCI	Vascular cognitive impairment
WMH	White matter hyperintensities

What this dissertation is about

Growing and aging populations implies increasing numbers of people with cognitive impairment and dementia. Alzheimer's disease (AD) is the most common dementia type, 60-80 % of those with dementia having AD [1]. AD consists of around 75 % sporadic late-onset AD (LOAD), 15-25 % familial LOAD and around 5 % early-onset AD (EOAD) (figure 1) [2-5]. EOAD comprises familial EOAD (<1 %) and sporadic EOAD (4-5 %) [6]. Age of onset is considered to be before the age of 60-65 years for EOAD and after the age of 60-65 years for LOAD [4,6-8]. After many years of preclinical disease activity, perhaps several decades, AD eventually brings about subjective memory complaints (SMC) and mild cognitive impairment (MCI) until manifesting itself as dementia [9].

Figure 1. Subclassification of AD



AD is a neurodegenerative disease with unclear etiology and pathophysiology. High age is the major known risk factor, secondly being a carrier of the ApoE ϵ 4 allele or being a member of a family with aggregation of AD [4].

There are many hypotheses about the pathophysiology of AD, the amyloid hypothesis being predominant since 1991 [8,10]. The amyloid hypothesis has not yet been proven, but also remains to be disproven [11]. An imbalance between production and clearance of A β 42 and related peptides leads to A β accumulation in the brain. This is an early or initiating factor of AD [8,12]. In dominantly inherited AD, missense mutations in the amyloid precursor protein (APP), presenilin 1 and presenilin 2 genes cause overproduction of A β 42. Dominantly inherited AD – familial EOAD – is rare, and constitutes less than 1 % of AD cases. In the most prevalent forms of AD, sporadic and familial LOAD, there is failure of A β clearance mechanisms [8].

Neuronal amyloid precursor protein (APP), an integral membrane protein consisting of 695 amino acids, is particularly expressed in the synapses. APP has been implicated as a regulator of synaptic formation and repair, and of anterograde neuronal transport [12]. In dominantly inherited AD, cleavage of APP first at position 1 by β secretase (amyloidogenic pathway) and then at position 42 by γ -secretase, leads to relative overproduction of the long more insoluble and toxic peptide $A\beta(1-42)$, commonly referred to as $A\beta_{42}$ (figure 2) [12]. Compared with shorter $A\beta$ peptides, including $A\beta_{40}$ which is most common, $A\beta_{42}$ enhances aggregation propensity, promoting accelerated formation of extraneuronal small $A\beta$ oligomers, protofibrils, fibrils and amyloid plaques [2,12,13]. The oligomeric form of $A\beta$ is considered to be most synaptotoxic. The deposited $A\beta$ has a high content of β -pleated sheet secondary structure. In the non-amyloidogenic pathway, APP is initially cleaved by α -secretase and subsequently by γ -secretase.

Figure 2. APP proteolytic pathways

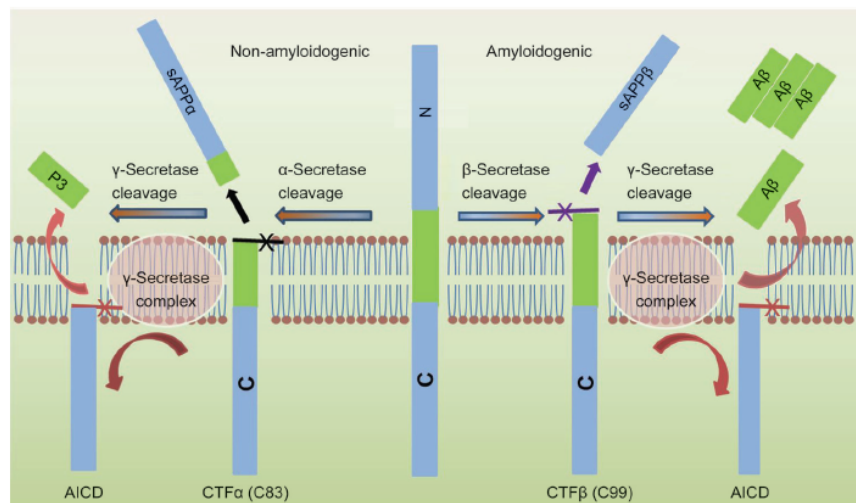


Figure 2. Human APP proteolytic pathways. Human APP proteolysis in the non-amyloidogenic pathway and amyloidogenic pathway. Non-amyloidogenic processing of APP refers to the sequential processing of APP by membrane bound α -secretases, which cleave within the $A\beta$ domain to generate the membrane-tethered α -C terminal fragment CTF α (C83) and the N-terminal fragment sAPP α . CTF α is then cleaved by γ -secretases to generate extracellular P3 and the APP intracellular domain (AICD). Amyloidogenic processing of APP is carried out by the sequential action of membrane bound β - and γ -secretases. β -Secretase cleaves APP into the membrane-tethered C-terminal fragments β (CTF β or C99) and N-terminal sAPP β . CTF β is subsequently cleaved by γ -secretases into the extracellular $A\beta$ and APP intracellular domain (AICD).

Figure: Chen et al., Acta Pharmalogica Sinica, 2017: 1205-1235 (permission granted from publisher)

There are several different types of amyloid plaques [14]. The amyloid plaque consists of an $A\beta$ core that to varying extents is surrounded by axonal and dendritic processes, $A\beta$ fibrils, glial cell processes and microglial cells. Amyloid plaques are the end result of a process of $A\beta$ oligomerisation, fibril formation, aggregation and precipitation, occurring in several stages, each stage potentially having a different impact on neurons in the vicinity [4].

According to the amyloid cascade hypothesis, A β -oligomers and A β -peptides promote hyperphosphorylation of intraneuronal tau protein (figure 3) [8]. Tau normally stabilizes and promotes the assembly of microtubules, facilitating the transport of intraneuronal products along the axon to synapses [4]. Hyperphosphorylated tau aggregates to form paired helical filament tau, causing disruption of the microtubules and aggregation into neurofibrillary tangles. This leads to dysfunctional neurons, synaptic loss and neuronal death.

A causal relationship between extracellular deposits of A β -peptides and damage on intraneuronal tau protein has not, however, been shown [11]. A β and tau protein are the primary constituents of the two hallmarks of AD, the amyloid plaque and the neurofibrillary tangle (NFT) [15].

Figure 3. The amyloid cascade hypothesis

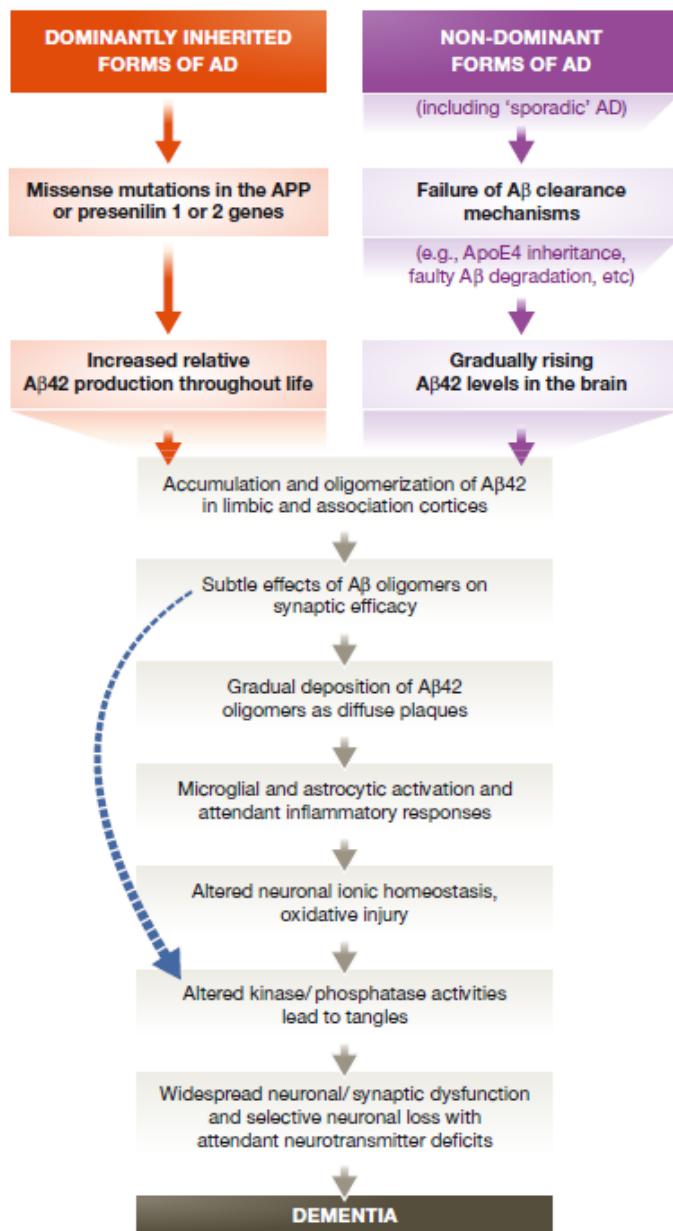


Figure 1. The sequence of major pathogenic events leading to AD proposed by the amyloid cascade hypothesis.
 The curved blue arrow indicates that Aβ oligomers may directly injure the synapses and neurites of brain neurons, in addition to activating microglia and astrocytes.

Figure: Dennis Selkoe and John Hardy, EMBO Molecular Medicine, Vol. 8, No. 6, 2016
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The ApoE gene is located on chromosome 19, and has three alleles - ApoE ε2, ApoE ε3 and ApoE ε4. The ApoE ε4 allele was recognized as a risk factor for LOAD in 1993 [16]. Studies suggest that carriers of one ε4 allele (ε4 heterozygous) have two- to threefold increased odds of AD, whereas carriers of two ε4 alleles (ε4 homozygous) have 8-fold to 12-fold increased odds of AD compared with

noncarriers [17]. The ApoE ϵ 4 allele may also impede cholinergic functions by reducing choline acetyltransferase activity and exacerbate the effects of cerebrovascular risk factors on cognitive function [18].

The ApoE gene is considered to be a susceptibility gene for LOAD. The ApoE ϵ 4 allele is neither necessary nor sufficient for the development of LOAD, up to 50 % of AD patients not possessing the ApoE ϵ 4 allele [19]. This indicates that the ApoE ϵ 4 allele in combination with other genes and environmental risk factors can increase the risk of LOAD.

Apolipoprotein E (ApoE) is strongly expressed in the brain and liver, and transports lipids, including cholesterol, throughout the cerebrospinal fluid (CSF) and plasma [18]. ApoE is synthesized by astrocytes and microglia and by neurons following injury. ApoE has a key function in supplying cholesterol for the development, maintenance and repair of myelin, neuronal membranes and synaptic connections. The three common isoforms of ApoE (ApoE ϵ 2, ApoE ϵ 3 and ApoE ϵ 4) are coded for by the alleles, ϵ 2, ϵ 3 and ϵ 4 respectively. ApoE ϵ 3 is the most common isoform and ApoE ϵ 2 the rarest. The isoforms differ profoundly in their ability to interact with A β . Increasing ϵ 4 allele dose is associated with reduced clearance and increased accumulation of A β [18].

Vascular dementia (VaD) is the second most common dementia type. In Europe, 10-20 % of dementia cases have VaD [20]. Cerebral small vessel disease (CSVD) is the most prevalent cause of VaD [4,21,22]. Vascular cognitive impairment (VCI) refers to all forms of cognitive disorder associated with cerebrovascular disease [23]. VCI and VaD can occur in connection with cerebral strokes, while VCI due to CSVD usually manifests gradually, appearing as vascular mild cognitive impairment (vMCI) before manifesting itself as VaD (figure 4) [24].

Figure 4. Gradual versus rapid development of VCI and VaD

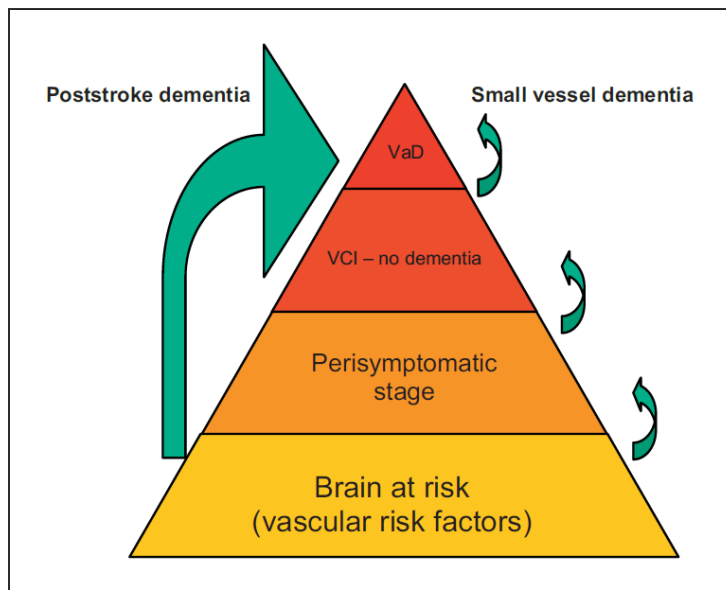


Fig. 1. The pyramid of VCI.

Figure: Pantoni et al., *Cerebrovascular Diseases*, 2009;27(suppl 1):191–196
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CSVD can appear as lacunes, white matter hyperintensities (WMH), microbleeds and increased perivascular spaces on MRI [22]. CSVD is associated with diffuse ischemic damage and cognitive dysfunction particularly in executive function and attention [25].

Cardiovascular risk factors are not only risk factors for CSVD and large vessel disease in VaD, but may also be risk factors for AD (figure 5) [26,27]. AD and CSVD often coexist in dementia and there appears to be a considerable overlap between AD and vascular disease. Dementia that is considered to be caused by both is termed mixed dementia [4]. It has been shown that appr. 34 % of patients with AD have mixed dementia [28]. ApoE leakage induced by CSVD has been associated with AD and accumulation of A β in perivascular astrocytes and transient induction of A β deposition [29]. Age related changes on cerebral arteries may impair drainage of soluble A β , which in turn leads to A β accumulation in vessel walls and brain parenchyma.

Figure 5. Determinants of VCI

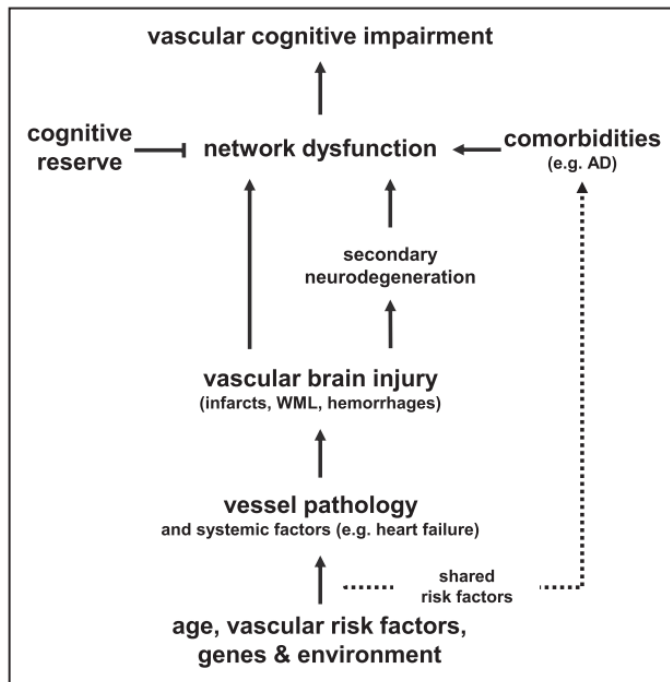


Figure 4. Key determinants of vascular cognitive impairment.

Figure: Dichgans and Leys, *Circulation Research*, 2017 Feb 3;120(3):573-591

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There are no biomarkers that can diagnose AD early, nor treatments that can curb, halt or cure AD. More knowledge about AD is therefore urgently required, the primary goal being to discover the etiologies and disease mechanisms underlying AD, to find treatments that can break the chain of events and halt the disease. Disease modifying treatments for AD clearly constitute inferior goals [30]. So far, different approaches aimed at inhibiting disease progression of AD with disease modifying treatments have failed to document beneficial effects [31,32]. The lack of good biomarkers for AD is an issue in this context, making it difficult to accurately quantify the effects of disease modifying treatments.

LOAD has different causal factors and can have several different etiologies with similar presentation clinically, on brain imaging and histologically [33,34]. LOAD is considered to be a complex multifactorial disease with a number of genetic, epigenetic and environmental risk factors [35-39]. There are connections between cerebrovascular disease and LOAD, as well as differences between sporadic and familial LOAD [4,40,41].

In stroke free persons from a general population (papers I-III), we wanted to test associations between cardiovascular risk factors and cognitive function.

Moreover, we wanted to test whether mild cognitive impairment (MCI) in persons with probable prodromal sporadic LOAD differs from MCI in persons with probable prodromal familial LOAD.

Paper I was a cross-sectional case-control study of 103 cases and 58 controls. Fully automated magnetic resonance (MR) volumetry of cerebral structures was carried out on persons with MCI who came from families with aggregation of LOAD (these cases were considered to have probable prodromal familial LOAD), on persons with MCI from families without LOAD (these cases were considered to have probable prodromal sporadic LOAD) and on controls.

Volumetric measurements on persons with MCI and probable prodromal familial LOAD, and persons with MCI and probable prodromal sporadic LOAD were compared to controls and each another.

In a prospective study (paper II), in 1577 stroke-free subjects, we tested whether albuminuria and carotid atherosclerosis in 1994 predicted cognitive function in 2007.

In a cross-sectional case-control study (paper III) with 140 cases and 58 controls, we tested associations between cardiovascular risk factors, the ApoE ϵ 4 allele and parental LOAD on the one hand, and fully automated MR volumetric findings on the other. Besides, whether fully automated MR volumetric findings could distinguish 25 cases with subjective memory complaints (SMC) and 115 cases with MCI from controls.

In the cross-sectional case-control studies (papers I and III), we gathered thorough information on the dispersion of probable LOAD in the participants' families. Furthermore, we had comprehensive data on cognitive function, cardiovascular risk factors, ApoE genotype and fully automated MR volumetry of cerebral structures for all participants. Research on AD and CSVD that has incorporated all these variables has been sparse, and there has been none in Norway.

Introduction and background

Dementia is, after cardiovascular disease, the leading cause of death in older adults [42]. The major causes of dementia are, in declining order, AD, cerebrovascular disease, dementia of Lewy bodies (DLBD) and frontotemporal dementia (FLD) as shown in figure 6 [1]. They are all, with the exception of cerebrovascular disease, neurodegenerative diseases [43-45]. Worldwide, about 40 million people have dementia, a number that is expanding and expected to double in 20 years [43,46].

In Europe, about 6 % of the population over the age of 65 has dementia [47]. In Norway, with its 5.3 million inhabitants, only crude estimates exist of how many persons have dementia. According to "Aldring og Helse" (a Norwegian governmental health agency), probably 70 000-104 000 Norwegians have dementia. The personal and societal toll of dementia is obvious. In Norway, around 80 % of

nursing home residents and more than 40 % of people over 70 receiving domiciliary care have dementia [48].

Figure 6. Prevalence of the major dementia types

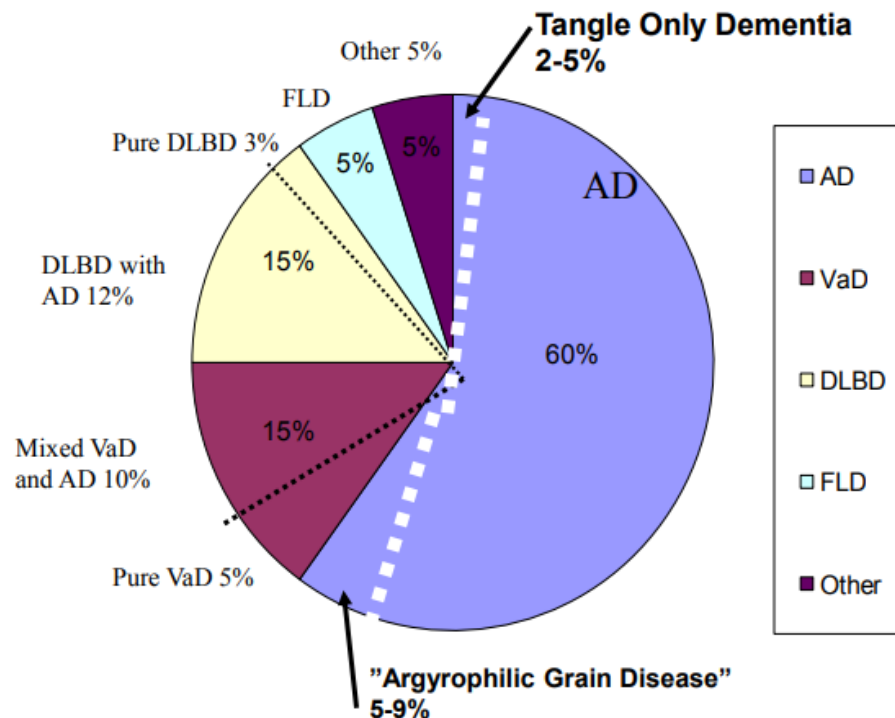


Figure: The major dementia types in persons over the age of 75 (permission granted from professor Nenad Bogdanovic, Karolinska Institutet, Stockholm)

Our focus in the Tromsø Dementia Study (papers I and III) is primarily on LOAD – sporadic versus familial – and CSVD. Studies have shown that there may be connections between vascular and AD pathology in the evolution of clinical VCI and AD [49]. We wanted to assess the roles of cardiovascular and genetic risk factors in persons from a general population. Other diseases or conditions that cause dementia are therefore not discussed.

Cognitive impairment and dementia

Dementia due to AD and CSVD is the result of long term processes lasting 20-30 years or more [50]. When a person gets the impression of having cognitive impairment, without others noticing it and achieving normal scores on cognitive testing, the condition can be referred to as subjective memory complaints (SMC), subjective cognitive decline or subjective cognitive impairment [51-54]. This does not necessarily represent neurodegenerative disease or CSVD, but can have a number of causes, particularly depression [55]. When SMC stems from a neurodegenerative disease such as AD, representing a prodromal stage of AD, MCI and dementia develops subsequently (figure 7) [9]. MCI is

defined as a cognitive decline greater than that expected for age and education, and which does not interfere notably with daily activities [56]. Dementia represents a gradual cognitive decline so large that it interferes notably with daily activities. Different sets of criteria are employed to diagnose and distinguish between AD, vascular dementia and other dementia types. For instance, there are NINCDS-ARDRDA criteria, ICD-10 criteria and the DSM criteria for AD, and own DSM criteria and ICD-10 criteria as well as the NINDS-AIREN criteria for probable vascular dementia [57-60]. The different sets of criteria for dementia have in common that there must be cognitive impairment in at least two cognitive domains.

Figure 7. Progression of AD and cognitive impairment

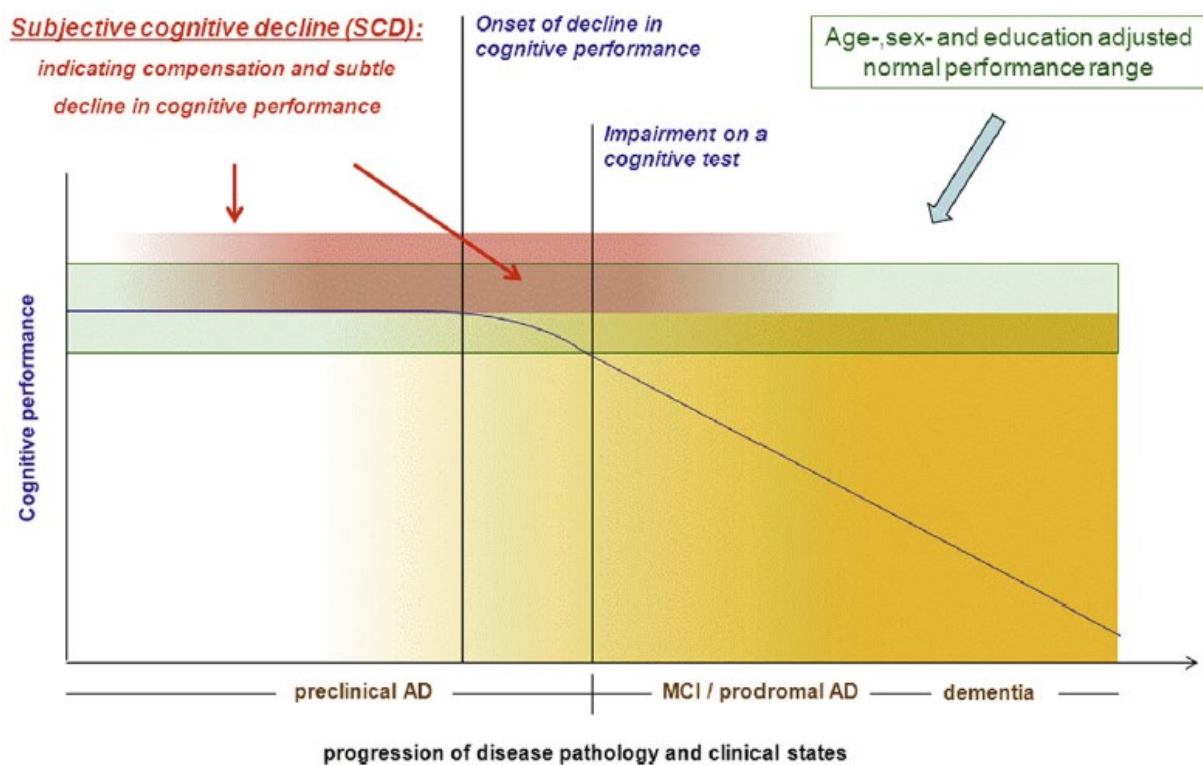


Figure: Jessen et al., Alzheimer's Dementia, 2014;10(6):844-52

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Risk factors and risk markers

Cardiovascular risk factors are considered to be risk factors for CSVD, and are suggested to also be risk factors for AD [49,61-65]. Homocysteine (Hcy) appears to be a risk factor for both VaD and AD [66,67]. However, the roles of cardiovascular risk factors and homocysteine in CSVD and AD have not been sufficiently clarified.

Many genetic risk factors for AD have been discovered. Mutations in the amyloid precursor protein (APP) gene and the presenilin genes (PSEN1 and PSEN2) are fully penetrant and bring about familial

EOAD, age of onset typically being between 30-60 years. However, less than 1 % of patients with AD have these mutations, and most EOAD patients are sporadic [68]. Epidemiological studies of EOAD indicate that the vast majority are non-familial, accounting for about 4–6 % of all AD [69].

The most common form of AD, LOAD, occurs most often sporadically as sporadic LOAD, but also recurs in families as familial LOAD. Familial LOAD can be defined as two or more biological family members having LOAD [4,70]. Members of families with an aggregation of LOAD, i.e. familial LOAD, have a considerably higher risk of developing LOAD [71]. After advanced age, having a first-degree family history of LOAD, especially when a parent is affected, is the most significant risk factor for developing LOAD [72]. The genetically mediated risk in familial LOAD is only partially explained by the ApoE ϵ 4 allele, which is found in less than 40 % of persons with familial LOAD [70]. Familial and sporadic LOAD might therefore differ in causal factors and pathophysiology [72,73].

The ApoE ϵ 4 allele is the major known genetic risk factor for LOAD. In a recent study by Cruchaga et al., polygenic risk score of sporadic LOAD revealed a shared architecture with familial LOAD, sporadic EOAD (age of onset <65 years without documented familial history of AD) and familial EOAD [6]. Sporadic and familial LOAD still largely constitute a genetic conundrum [43,74-80]. The ϵ 4 allele brings about a dose-dependent increase in the risk of developing LOAD [18]. In ApoE ϵ 4 homozygotes the lifetime risk for LOAD is more than 50 %.

ApoE is essential for normal lipid homeostasis in the brain, and ApoE isoform might influence several physiologic pathways [18]. ApoE is produced in many tissues, such as in the brain, skin, liver, spleen and kidneys, and maintains the structural integrity of lipoproteins and facilitates their solubilization in the blood [81,82]. The ϵ 4 allele may cause a gain of toxic function in the ApoE protein, or loss of neuroprotective function, or both [18]. The consensus is that differential effects of ApoE isoforms on A β aggregation and clearance, play a major role in LOAD pathogenesis.

Most of the known genetic risk factors constitute only a minimal or low risk for LOAD (figure 8) [43]. Genome-wide association studies, together with exome and genome sequencing, have pointed out three particularly important biological processes in AD pathogenesis [8]. These are cholesterol metabolism, endosomal recycling and inflammation and the brain's immune system (figure 8) [43]. A polygenic hazard score based on known single-nucleotide polymorphisms in genes linked to AD, has recently been developed to quantify individual differences in age-specific genetic risk for AD [83].

Figure 8. Genes linked to AD

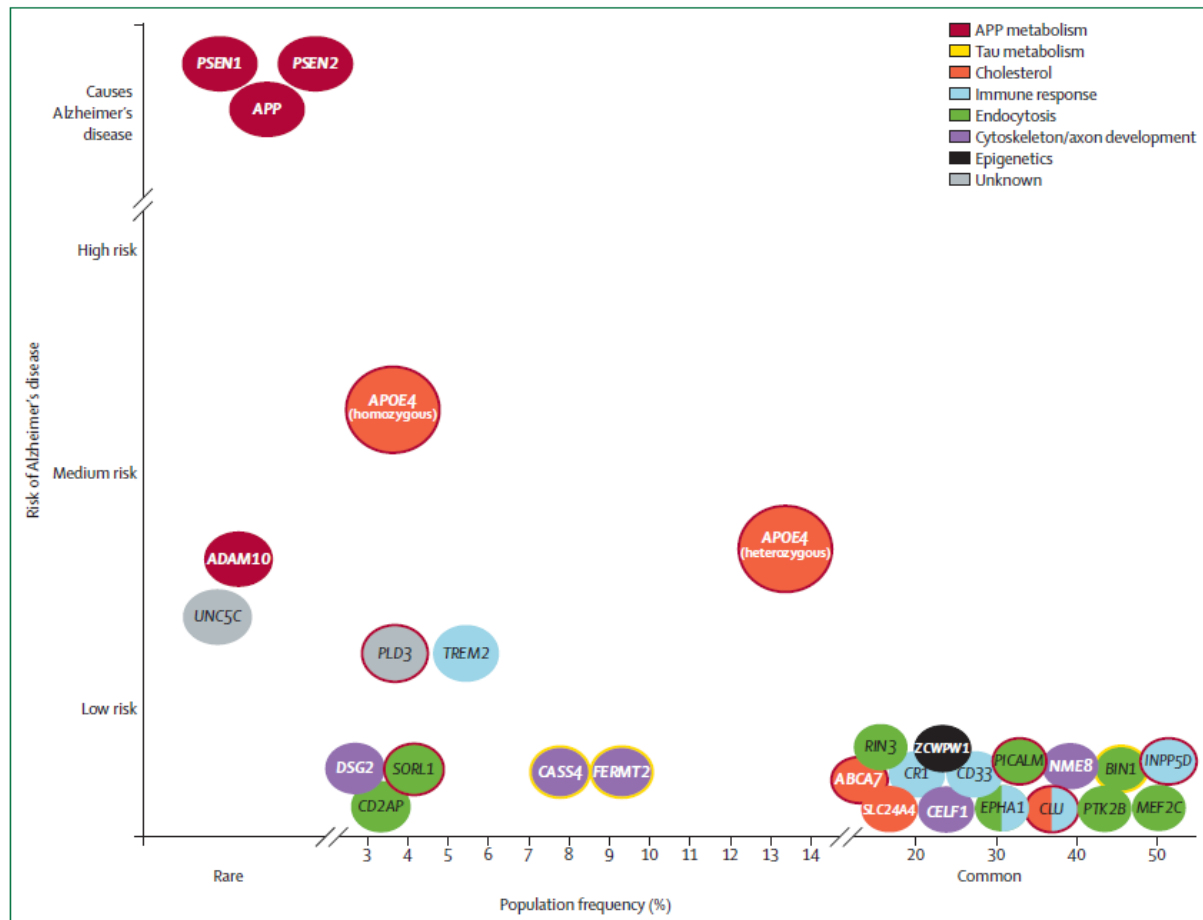


Figure: Schematic overview of genes linked to Alzheimer's disease

The colours in the key show the pathways in which these genes are implicated. Genes that are known to affect APP metabolism are circled in red, whereas those that affect the tau pathway are circled in yellow. The interior colours provide further information on what functions the genes have. When there are two colours, the gene might have functional roles in two different biological pathways. Many of the genes have been related to APP processing or trafficking (red or red border), suggesting the central importance of APP metabolism in Alzheimer's disease. The figure was adapted with permission from Karch et al, 2015.³⁹

Figure: Scheltens et al., The Lancet, Vol. 388, July 30, 2016 (permission granted from publisher)

Albuminuria is a surrogate marker of endothelial dysfunction and microvascular disease anywhere in the circulation [84]. It is a risk marker of renal endothelial dysfunction, chronic kidney disease and cardiovascular disease [85]. Albuminuria and endothelial dysfunction are considered to be precursors of atherosclerosis [86]. Albuminuria might also be a risk marker of cerebral endothelial dysfunction and vascular cognitive impairment (VCI) [84,87]. The brain and the kidneys are both highly vascularized end organs and share hemodynamic characteristics. Albuminuria might therefore express cerebral endothelial dysfunction [87,88].

Ultrasonography of the internal carotid arteries gives measurements of intima-media thickness (IMT) and total plaque area (TPA). Several prospective studies have shown that subclinical carotid atherosclerosis is inversely associated with cognitive function [89]. Increased IMT and TPA, besides

being risk factors for intracerebral vascular disease, are potential risk markers of cognitive decline [89].

Biomarkers

Biomarkers can detect AD at different stages of the disease course, as shown in figure 9 [8]. They can also assess the amount of cerebrovascular disease [23,90].

Cerebral imaging and analysis of CSF are performed to assess biomarkers of AD in the clinical routine [43]. The core CSF biomarkers are A β 42, phosphorylated tau (p-tau) and total tau (t-tau). Due to inadequate sensitivity and specificity, the core CSF biomarkers are not suitable for wide clinical implementation [91]. They are unable to distinguish satisfactorily between the dementia subtypes or predict transition between the different stages of cognitive impairment. Hence, lumbar puncture and measurement of cerebrospinal fluid A β 42, t-tau and p-tau are carried out to varying extents clinically. However, quantification of the core CSF biomarkers is routinely used in memory clinics and to enrich study and trial samples [91,92].

Computed tomography (CT) imaging and magnetic resonance imaging (MRI) of the brain are the main imaging modalities in the clinical routine for cognitive impairment. They can detect other intracranial causes of cognitive impairment, for example idiopathic normal pressure hydrocephalus, tumors and stroke, and assess the amount of cerebrovascular disease [23,43,93]. Several visual rating scales that estimate for instance atrophy of cerebral structures, are applied to diagnose dementia and distinguish between dementia subtypes [94]. In AD and frontotemporal dementia, cerebral structures atrophy in a characteristic temporal pattern [93,95].

MRI has better resolution than CT imaging, and is utilized in the early diagnosis of AD and frontotemporal dementia [93,96-98]. In AD, MR volumetry can show distinct changes in hippocampus, amygdala, lateral ventricles and medial temporal lobes [96-98]. Atrophy of association cortices in the temporal, frontal and parietal lobes occurs later in the course of AD [99]. Features of CSVD shown on MRI include WMH, small subcortical infarcts, microbleeds, lacunes, perivascular spaces and brain atrophy [90].

Promising MRI research techniques to visualize CSVD and its lesions include ultra high field strength MRI (>3.0 Tesla), diffusion tensor imaging of detailed structural connectivity and magnetisation transfer assessment of white matter myelination [90].

The prevailing view is that AD has its origin in the transentorhinal and entorhinal cortex of the medial temporal lobes, and subsequently spreads to other locations. However, it is possible that neurodegeneration starts simultaneously in other locations, including the nucleus basalis of Meynert

located deep in the frontal lobes and the locus coeruleus located in the pons of the brainstem [95]. The nucleus basalis of Meynert provides the single major source of cholinergic innervation to the entire cerebral cortex [100]. The locus coeruleus' is the major noradrenergic nucleus of the brain. Its efferent fibers are highly branched and reach virtually all parts of the central nervous system [34]. The nucleus basalis of Meynert and the locus coeruleus have in common that they send fibers directly to the cerebral cortex, without synaptic interruption in the thalamus [34].

Manual MRI-volumetry of cerebral structures is not cost-effective as it is too time-consuming. Fully automated brain volumetry has therefore been developed to help diagnose AD and frontotemporal dementia in the clinical routine [93,101-103]. The fully automated volumetric software NeuroQuant can back up other clinical investigations in diagnosing AD [104-106].

Positron emission tomography (PET) imaging is important in AD research, for example to enrich study and trial samples. It is, however, not yet cost-effective in the clinical diagnostic work-up of cognitive impairment [91,107-109]. PET amyloid imaging using the tracer Pittsburgh Compound-B (PiB) suggests that 20-30 % of cognitively normal persons have positive PiB scans, while about 60 % of persons with MCI have positive PiB scans [110]. Fluorodeoxyglucose (FDG) PET can measure glucose hypometabolism in the brain. Synaptic activity in the brain is associated with glucose metabolism, persons with AD showing a characteristic pattern of hypometabolism in the temporoparietal regions bilaterally [4].

The ApoE ϵ 4 allele is the major known genetic risk factor for LOAD, and a biomarker for AD [111]. However, it has little clinical applicability, as it only to a limited extent predicts cognitive decline or conversion to AD [112].

Figure 9. Temporal model of AD biomarkers

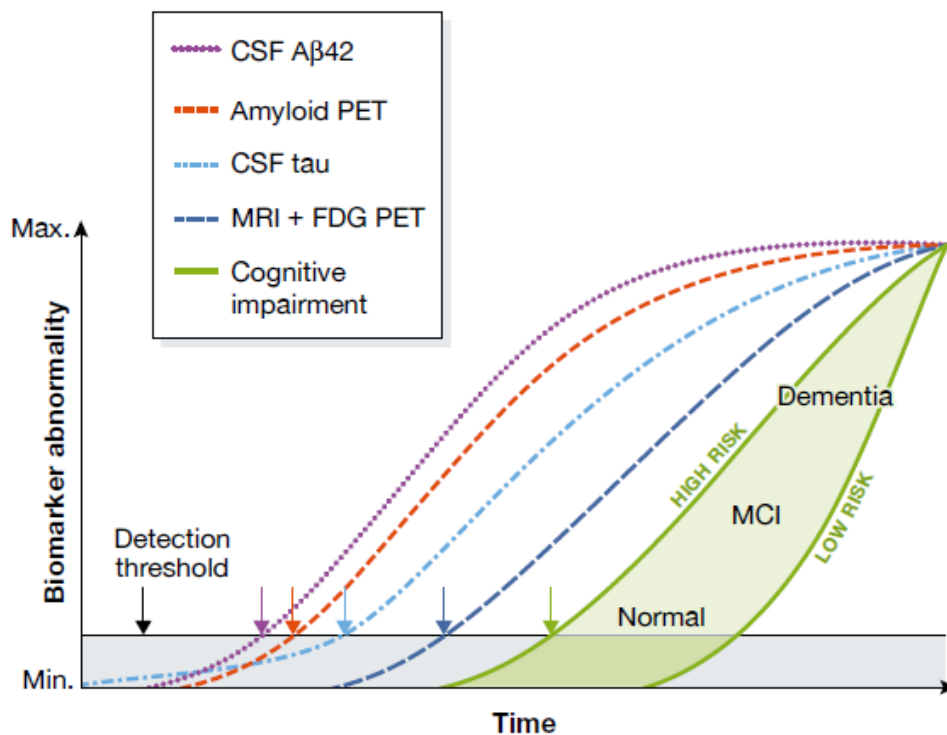


Figure 3. A hypothetical temporal model integrating Alzheimer's disease biomarkers.

The threshold for the first detection of biomarkers associated with pathophysiological changes is denoted by the black horizontal line. The gray area denotes the zone in which abnormal pathophysiological changes lie below this biomarker detection threshold. In this model, the occurrence of tau pathology can precede A β deposition in time, but only early on at a sub-threshold biomarker detection level. A β deposition occurs independently and rises above the biomarker detection threshold (purple and red arrows). This induces acceleration of tauopathy, and CSF tau then rises above the detection threshold (light blue arrow). Later still, changes in FDG PET and MRI (dark blue arrow) rise above the detection threshold. Finally, cognitive impairment becomes evident (green arrow), with a wide range of cognitive responses that depend on the individual's risk profile (light green-filled area). Note that while CSF A β 42 alteration is plotted as a biomarker (purple), this represents a decrease in CSF A β 42 levels and is a surrogate for an increase in parenchymal A β 42 and changes in other A β peptides in the brain tissue. A β , amyloid β -protein; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment. (Adapted from Fig 6 of Jack *et al*, 2013.)

Figure: Dennis Selkoe and John Hardy, EMBO Molecular Medicine, Vol. 8, No. 6, 2016 (permission granted from publisher)

Aims of the thesis

This thesis consists of three papers. A primary aim was to test associations between cognitive function on the one side, and cardiovascular and genetic risk factors on the other, in a general population.

The specific aims were:

- to test whether tHcy, cardiovascular risk factors and fully automated MR volumetric measurements of cerebral structures in persons with MCI differ between persons from families with or without probable familial LOAD. **Paper I**

- to test whether albuminuria and carotid atherosclerosis independently predict cognitive function 13 years later. **Paper II**

- to test whether fully automated MR volumetric findings were associated with probable parental LOAD, ApoE ϵ 4 genotype, tHcy and cardiovascular risk factors and to also test whether fully automated MR volumetry of cerebral structures could distinguish persons with SMC and MCI from cognitively healthy controls. **Paper III**

Materials and methods

All subjects and data in this thesis are from the Tromsø Study. The Tromsø Study started in 1974 with its first survey, Tromsø 1, primarily to address cardiovascular diseases that at that time constituted an overwhelming health problem. Every 6-7 years the Tromsø Study has a new survey, and the last, Tromsø 7, was in 2015-2016.

Since Tromsø 4 (1994-95), the survey has had two visits, with a more comprehensive examination in the second visit. Eligible candidates for the second visit are decided already before the first visit.

Gradually, other conditions and chronic diseases gained attention, such as cognitive impairment and AD. Cognitive testing was introduced in Tromsø 5 (2001-2002), and has since been a part of the second visit in the Tromsø Study. The Tromsø Study cohort has been described earlier [113].

All Tromsø Study participants are from the municipality of Tromsø. The number of inhabitants increased gradually from appr. 42 000 inhabitants in 1974 to 65 000 inhabitants in 2008. In Tromsø I,

8866 men were invited to the survey, whereof 6959 attended. In Tromsø 6 (2007-08), 19762 persons were invited, whereof 12984 attended.

The University hospital of North Norway, which is located in Tromsø, is the only hospital in the region. The next-nearest hospital is 250 km away. Relevant data on Tromsø Study participants can be easily accessed and the cohort of the Tromsø Study is therefore well characterized.

The Tromsø Dementia Study (papers I and III) is a cross-sectional nested case-control study in Tromsø 6. Paper II presents a prospective study based on data on subjects who participated in the second Tromsø 4 and Tromsø 6 visit.

Ethics

Persons who answered "Yes" to the question "Has your memory declined" in the Tromsø 6 first visit questionnaire were potential cases for the Tromsø Dementia Study. Neurodegenerative diseases lack effective treatment. It would therefore be unethical to diagnose cognitive impairment and potential neurodegenerative disease in those who do not suspect they are suffering from these conditions.

The Tromsø Dementia Study (papers I and III) and the prospective study (paper II) were approved by the board of the Tromsø Study and the Regional Ethical Committee of Northern Norway. The Tromsø Dementia Study was also approved by the Norwegian Social Science Data Services.

Study population paper I

A total of 19 762 persons were invited to the first Tromsø 6 visit, 12 984 taking part. Those who fulfilled the following criteria were invited to take part in more comprehensive testing in the second visit: first visit participants aged 50-62 and 75-84 years, a 20 % random sample of men and women aged 63-74 years and subjects who had attended the second examination in Tromsø 4 and were aged <75 years in 1994. Out of 11484 eligible participants, 7307 attended the second visit.

The following is a brief description of the population, including some supplemental information. The second Tromsø 5 visit included three cognitive tests: the finger-tapping test (FTT), the digit-symbol coding test (DST) and the twelve word test which is comprised of two parts [114-116]. The 2.5 percentile of these cognitive test scores were defined as cutoff values for low cognitive test scores for the second Tromsø 6 visit. Low test scores were therefore <4 for the word test part 1, <5 for the word test part 2, <23.0 for the FTT and <12 for the DST. The Mini Mental State Examination (MMSE) was introduced in Tromsø 6 and has by definition a low test score of <24 [117].

Persons who answered "Yes" to the question "Has your memory declined" on the Tromsø 6 first visit questionnaire and had one or more low cognitive test scores in the second Tromsø 6 visit were eligible as cases for the Tromsø Dementia Study. Persons who answered "No" to the question "Has

your memory declined?" and who had cognitive test scores above the cutoff values in the second Tromsø 6 visit were eligible as controls.

Eligible cases were invited by mail to take part in the Tromsø Dementia Study. They were informed of having achieved low cognitive testing scores and that they were therefore of interest as participants in cognitive impairment research. The letter informed them that in addition to comprehensive cognitive testing, a cerebral MRI would be performed and a blood sample would be drawn during the visit. Totally, 403 eligible cases were invited, whereof 139 assented. Eligible controls matched for sex and age were at the same time invited by mail. They were informed of having achieved normal cognitive testing scores and were therefore of interest as controls in cognitive impairment research. They were also informed about cognitive testing, cerebral MRI and the drawing of a blood sample. A total of 180 were invited, 73 taking part.

Cases and controls with stroke (not lacunar) on cerebral MRI were excluded. The number of cases and controls diminished to 103 and 58 respectively due MRI results and cognitive testing in the Tromsø Dementia Study. This is shown in figure 1 of the paper. The remaining cases were considered to have probable prodromal sporadic LOAD, familial LOAD or to be intermediary and to also possibly have coexisting CSVD.

The participants were classified into four groups. The controls were in group 1. Group 2 consisted of cases without knowledge of any biological relatives with LOAD. These were considered to have probable prodromal sporadic LOAD. Group 3 consisted of cases who had one biological relative with LOAD with onset of LOAD after the age of 65. Group 4 consisted of cases with ≥ 2 biological relatives on one side of their family with the onset of LOAD after the age of 65. The cases in group 4 were considered to have probable prodromal familial LOAD.

Group 4 in an alternative classification of groups 3 and 4 consisted of cases with a parent or parents with LOAD. These cases were considered to have probable prodromal familial LOAD based on less, but more reliable information. Group 3 then consisted of cases with other biological relatives with LOAD.

Study population paper II

All persons aged ≥ 25 years were invited to the first Tromsø 4 visit, 27 159 persons taking part. All participants between age 55 and 74 and 5-10 % representative samples of the other birth cohorts aged 24-84 years (9 057 in total) were invited to the second visit, 7 965 taking part. In Tromsø 4, analysis of albuminuria and ultrasound examination of the right internal carotid artery were introduced as part of the second Tromsø Study visit.

Eligible persons were those who had taken part in both Tromsø 4 and Tromsø 6, had albuminuria and ultrasound examination of the right internal carotid artery results, blood tests results and Tromsø 4 and Tromsø 6 questionnaire information on vascular risk factors. Moreover, they had to have cognitive test results from Tromsø 6 DST and FTT. Exclusion criteria were self-reported stroke or missing information on self-reported stroke in Tromsø 6, and macroalbuminuria in Tromsø 4 or Tromsø 6. Figure 1 in paper II provides a detailed description of the selection of participants.

Study population paper III

The sample consists of 12 additional cases with MCI and 25 cases with subjective memory complaints (SMC), all being in addition to the cases and controls of paper I.

Of the 12 extra cases with MCI, 6 cases were not included in paper I because of incomplete information on probable LOAD in second and third-degree relatives and 6 cases were not included because they had reported an earlier stroke which there were no signs of on MRI. These 12 cases were now included because information on LOAD in second and third-degree relatives was not necessary and because they probably had not had a stroke, MRI showing no signs of this.

MMSE was introduced for the first time in Tromsø 6. The study personnel who administered the cognitive tests were new to this examination. This may account for testing of delayed recall in MMSE being unintentionally not carried out upon many of the second Tromsø 6 visit participants, which resulted in apparently low MMSE scores. Unfortunately, this passed unnoticed until the survey had ended. Participants with MMSE score <24 and with missing delayed recall testing, who answered "Yes" to "Has your memory declined" in the Tromsø 6 questionnaire and had normal scores on the finger tapping test, digit symbol coding test and twelve word test therefore appeared to be eligible cases. Several of these were therefore invited to and took part in the Tromsø Dementia Study. They could not, however, be confidently defined as cases. Some of them also had other missing variables in the MMSE, such as abstract thinking and subtractions.

In the event of missing results from cognitive testing in the second visit of Tromsø 6 – among other considerations – repeated cognitive testing had been implemented in the Tromsø Dementia Study. All these participants with missing MMSE scores in the MMSE in Tromsø 6, had MMSE scores >24 in the Tromsø Dementia Study. They achieved, on average, higher scores than the true cases with MCI in Tromsø 6. We therefore chose to define these 16 participants as having subjective memory complaints (SMC). The mean MMSE score was 28.9 for the 58 controls, 27.8 for the 16 SMC cases and 26.9 for the 115 MCI cases in the Tromsø Dementia Study.

The remaining 9 cases in the SMC group had, in error, been invited as cases to the Tromsø Dementia Study because of their DST scores. They answered "Yes" to "Has your memory declined" in the

Tromsø 6 questionnaire, but had DST scores that ranged from 12 to 16 (mean score 13.7) which was between the 2.5 and the 7.5 percentiles of the DST score for Tromsø 5. We therefore chose to define these 9 participants as also having SMC.

Papers I and III – The Tromsø Dementia Study

Cases and controls attended the Tromsø Dementia Study in the period April 2008-June 2009, which was within a few months after the second Tromsø 6 visit. A geriatrician and a research nurse administered the study. They invited cases and controls, carried out interviews, cognitive testing, physical examinations, drawing of blood samples and scheduled cerebral MRI appointments. The number of participants received each day was 3-4, which was the number of MRI slots the radiological department at the University Hospital of North Norway had available for the study. All but a few participants were accompanied by a family member or friend who could validate the participant's information and answer questionnaires on collateral information. In unaccompanied participants, questionnaires concerning collateral information were answered later by relatives and returned by mail. Data on blood pressure, body mass index (BMI) and smoking, were obtained from Tromsø 6 [113].

Interviews

All participants underwent structured interviews, nearly all being witnessed by a companion. They were interviewed in detail about their education, sensory impairment, gait and motility, medication, alcohol and drugs usage, social and physical activities, earlier diseases and specifically about diseases or conditions that could cause or resemble cognitive impairment.

The Montgomery and Aasberg dementia rating scale (MADRS) was applied to assess depression in all participants [118].

Petersen's original construct for MCI was applied [56]. We did not use later constructs with amnesic and nonamnesic subtypes of MCI [119]. The NINCDS-ADRDA criteria for AD were applied [120].

Cases and controls were interviewed in detail about whether they had biological relatives with probable LOAD. They were asked how many brothers and sisters they, their parents and maternal as well as paternal grandparents had. They were then asked how many of their relatives had or had had probable AD after the age of 65. They were specifically asked whether relatives with dementia might have or have had other conditions or diseases that cause dementia, such as a stroke or Parkinson's disease. Cases with MCI (paper I) were classified into three groups based on this mapping of the dispersion of probable LOAD. Those who had no relatives with probable LOAD were considered to have probable prodromal sporadic LOAD (group 2). Those with 2 or more biological relatives with

probable LOAD were considered to have probable prodromal familial LOAD (group 4) and those with 1 biological relative with probable LOAD (group 3) were considered to be intermediate.

In an alternative classification of cases with biological relatives with probable LOAD (cases in groups 3 and 4), cases with one or two parents with probable LOAD formed group 4, and were considered to have probable prodromal familial LOAD. Cases with other biological relatives with probable LOAD formed group 3, and were considered to be intermediate.

In paper III, cases and controls were classified as either having had one or two parents with probable LOAD (probable parental LOAD) or as not having had parents with probable LOAD.

Cognitive tests

A wide range of cognitive tests are used to examine cognitive function [114]. There is, in dementia, a deterioration of higher cortical functions such as memory, learning, understanding, judgment, thought, language and orientation in time and place [121]. Numerous cognitive tests have been developed to detect deterioration of skills in these cognitive domains. The tests applied in the Tromsø Study and the Tromsø Dementia Study are ones widely used to diagnose MCI and dementia. The four cognitive tests used in the Tromsø Study (FTT, DST, MMSE and the 12-word test) were also applied in the Tromsø Dementia Study. The clock drawing test and the trail making tests were additional cognitive tests in the Tromsø Dementia Study.

FTT mainly tests psychomotor tempo [114,116,122]. Participants tapped as quickly as they could with their index finger on a key on the keyboard of a computer for 10 seconds. This was carried out four consecutive times with the right and left index finger. The first time was for practice and to become familiar with the exercise. The mean number of taps of the non-dominant index finger for the last three performances were used in the analyses.

DST tests psychomotor performance. Motor persistence, sustained attention, response speed, visuomotor coordination and incidental memory influences performance [114]. At the top of a sheet of paper were two adjoined rows of boxes, 9 boxes in each row. The boxes of the top row contain symbols, each being allocated to a number (from 1 to 9) in the bottom row boxes. Below this number-symbol key are several equivalent adjoined rows of boxes filled in with numbers but not symbols. In the practice round, participants wrote in the first seven blank symbol boxes the missing symbols associated with the numbers in the row below. After this they had 90 seconds to fill in as many symbols as possible in the blank symbol boxes [116]. The achieved number of symbols was used in the analyses.

MMSE is the world's most widely used cognitive screening tool. It is a global cognitive test that crudely tests different cognitive domains such as orientation to time and place, learning, recall, calculation, language and visual construction [114,117,121]. Test performance is influenced by age, education, language problems and test situation.

The 12-word test is a modification of the California Verbal Learning test [115]. Part one tests immediate recall, part two tests recognition. Participants were asked to remember a series of words presented to them. In part one, 12 nouns were presented to the participant consecutively from a booklet, one being displayed every 5 seconds. The examiner simultaneously read the word aloud. The participants had two minutes right after this to recall the words [116]. The score range for part one was therefore 0 to 12. In part two, 24 nouns were shown from a booklet in the same way as in part one. These nouns included the 12 nouns of part 1 intermixed with 12 other nouns. Participants replied for each word whether it had been presented or not in the first part. Each wrong answer was scored -1 and each correct answer was scored 1. The score range for part two was therefore -24 to 24.

The clock drawing test tests visuospatial ability. Performance is influenced by participants' attention, understanding of numbers and executive function [121,123]. There are many versions of the clock drawing test. We used a 7 item version, 7 being the best score and 0 the poorest.

The trail making test tests attention, cognitive flexibility, visuomotor tracking and executive function [114,121,124]. It is comprised of trail making A and trail making B. In trail making A, a line is drawn as quickly as possible between consecutively numbered circles, numbered 1 to 25. The numbered circles are randomly placed on a worksheet. In trail making B, numbered circles 1-13 and lettered circles A-L are randomly placed on a worksheet. A line is to be drawn as quickly as possible that alternates between consecutive numbers and letters. The line therefore starts with 1 and A and ends with 13 and L. The time needed to complete the tasks was used in the analyses.

Collateral information

Cases and controls who consented to participate in the Tromsø Dementia Study, received three questionnaires by mail on collateral information. The vast majority of questionnaires were answered by spouses or by other family members or friends.

The informant questionnaire on cognitive decline in the elderly (IQCODE) is the most commonly used informant dementia assessment [125,126]. The IQCODE's 16 questions compare present cognitive function to cognitive function 10 years earlier. Each answer is scored from 1 to 5. A score of 1 is best, and indicates a much better cognitive function now than 10 years earlier. A score of 3 indicates

unaltered cognitive function, and a score of 5 much worse cognitive function. A mean score of around 3.5 indicates cognitive impairment.

The rapid disability rating scale-2 (RDRS-2) assesses activities of daily living [127]. We used the Norwegian version, which uses the same 18 considerations but splits them into 21 items. They are scored 1-4, and outcome scores therefore range from 21 to 84, 21 representing the best functional level.

The behavior and mood disturbance (BMD) scale assesses behavioral and psychological symptoms in dementia [128]. It contains 20 questions on behavior and 13 questions on cognition. All answers are scored from 0 to 4, scores of ≤ 40 for behavior and ≥ 26 for cognition being considered to be normal.

Blood samples

Blood samples were drawn from all participants to test sedimentation rate, sodium, potassium, ApoE genotype, total plasma homocysteine (tHcy), cobalamin, folic acid, phosphate, ionized calcium, free thyroxine and thyroid stimulating hormone. Other blood test results were taken from the Tromsø Study. All blood samples were analyzed at the Department of Clinical Chemistry, University Hospital of North Norway.

Magnetic resonance imaging

Cerebral MRI was carried out on all participants, and served two purposes. The first was to reveal intracranial pathology, the second to carry out fully automatic volumetric measurements of cerebral structures using the software package NeuroQuant. In the statistical analyses, the volumetric measurements were surrogate markers for preclinical and prodromal AD.

Neuroquant has been validated against manually traced volumes and semiautomatic methods [129,130]. The volumes of cerebral structures were intracranial volume corrected to adjust for differences in brain size, by summing the bilateral volumes of each cerebral structure and expressing it as a percentage of the intracranial volume. Papers I and III provide more detailed information.

Paper II

All data in paper II is taken from Tromsø 4 and Tromsø 6 [113]. Main predictor variables were urinary albumin-creatinine ratio (ACR) and ultrasonographic measurements of right internal carotid artery intima media thickness (IMT) and total plaque area (TPA). ACR correlates well with the quantification of albuminuria in 24-hour urine collection [131]. The methodology for these measurements have been described previously [132,133]. Collection of urine samples for albumin and creatinine measurements and ultrasonography of the right internal carotid artery for measurement of IMT and TPA were performed in the second Tromsø 4 and Tromsø 6 visits.

The outcome variable was cognitive function in the second Tromsø 6 visit, primarily assessed by DST and FTT.

Trained nurses recorded height, weight and blood pressure. Information on education, antihypertensive treatment, alcohol consumption, smoking, diabetes mellitus and coronary disease was taken from Tromsø 4 questionnaires [113].

Statistical analyses

Characteristics were displayed as means (standard deviation), medians (interquartile range), numbers or percent. The independent t-test, the Mann-Whitney test and the chi-square test were used to calculate differences between groups. Linear regression was applied to test associations and analysis of covariance (ANCOVA) was used to compare groups.

Apo E genotype in papers I-II was coded as a binary variable, heterozygote or homozygote for the $\epsilon 4$ allele on the one hand or not having the $\epsilon 4$ allele on the other.

The statistical analyses in paper I and III were performed using SPSS version 18, and in paper II using SPSS version 22.

Paper I

Comparisons between the case groups (groups 2-4) and the control group (group 1) were performed using ANCOVA.

There was an interaction between gender and groups 1-4 for tHcy level. Analyses were therefore performed gender specific. Outcome variables were tHcy, volumes of cerebral structures and cardiovascular risk factors. Using tHcy as outcome variable, we adjusted for age, systolic blood pressure, serum cobalamin, serum folate, BMI, estimated glomerular filtration rate (eGFR) and diabetes mellitus [134]. Volumes of cerebral structures and cardiovascular risk factors were adjusted for age.

Paper II

The subjects were grouped into sex specific ACR quartiles based on Tromsø 4 ACR measurements. In ANCOVA, ACR, Δ ACR (ACR Tromsø 6 minus ACR Tromsø 4), IMT and Δ IMT (IMT Tromsø 6 minus IMT Tromsø 4) were ranked sex specifically because ACR, IMT and DST and FTT performance differ between genders [114,135,136]. ACR and Δ ACR were ranked into quartiles, and IMT and Δ IMT dichotomized into those below versus those at or above the sex-specific median. Adjusted for age, sex, education, blood pressure medication, alcohol intake and cardiovascular risk factors, ACR and Δ ACR quartiles 2-4 were compared with ACR and Δ ACR quartile 1 respectively. We also tested

whether there were significant differences on the cognitive test scores between those with the smallest and largest IMT, and between those with the smallest and largest Δ IMT.

Multivariate linear regression was applied to test whether ACR (Tromsø 4), Δ ACR, IMT (Tromsø 4) and Δ IMT predicted Tromsø 6 cognitive test scores. The analyses were adjusted for the same variables as in ANCOVA.

The correlation between IMT and TPA was high (Spearman's $r = 0.50$), and in multiple regression both had approximately equivalent F-changes. IMT was preferred in the analyses as it, in contrast to TPA, brought about an equal number of subjects in the subgroup analysis.

Paper III

In ANCOVA, we tested whether sex and age adjusted mean volumes of cerebral structures differed significantly between cases with SMC or MCI and controls.

Receiver operating characteristic analysis was used to test the diagnostic ability of fully automated volumetric measurements to distinguish cases with SMC and MCI from controls.

In linear regression, associations between volumes of cerebral structures on the one side, and tHcy, genetic risk factors and cardiovascular risk factors on the other were tested. There was a borderline significant interaction ($p = 0.070$) between sex and probable parental LOAD for hippocampal volume. In paper I, this interaction was significant ($p = 0.027$). Therefore additional analyses were performed with hippocampal volume as outcome, stratified by gender and probable parental LOAD.

Main results

Paper I – Women with MCI and probable prodromal familial LOAD differ from women with MCI and probable prodromal sporadic LOAD

Women with MCI and probable prodromal familial LOAD did not have significantly higher tHcy than controls, unlike the other case groups. Moreover, in contrast to women with MCI and probable prodromal sporadic LOAD, they had significantly smaller volumes of amygdala and hippocampus, and significantly larger volumes of the lateral ventricles than controls.

In the alternative classification of cases with probable prodromal familial LOAD, using the Bonferroni correction, women with MCI and probable prodromal familial LOAD had significantly smaller hippocampal volume than controls, women with MCI and probable prodromal sporadic LOAD and women with MCI in the intermediate group ($p = 0.001, 0.040$ and 0.003 , respectively).

Correspondingly, they had significantly larger lateral ventricular volumes than women with MCI and probable prodromal sporadic LOAD.

We found no significant differences between the groups using BMI, systolic blood pressure, total cholesterol, eGFR and HbA1c as outcome variables in ANCOVA.

In the sample, 37.3 % of the participants were carriers of the ApoE ϵ 4 allele (1.9 % ϵ 2/ ϵ 4 heterozygotes, 5.0 % ϵ 4/ ϵ 4 homozygotes and 30.4 % ϵ 3/ ϵ 4 heterozygotes). In groups 1-4 in women, 46 %, 27 %, 39 % and 47 % respectively were carriers of the ApoE ϵ 4 allele. Correspondingly, in groups 1-4 in men, 39 %, 41 %, 17 % and 33 % respectively were carriers of the ApoE ϵ 4 allele. In groups 1-4 in women, in the alternative classification, 46 %, 27 %, 50 % and 38 % respectively were carriers of the ApoE ϵ 4 allele.

Women with MCI were more likely than men with MCI to have biological relatives with probable LOAD. In both genders, more than 65 % of the biological relatives with probable LOAD in groups 1, 3 and 4 were women.

Paper II – Albuminuria, carotid atherosclerosis and smoking are early and independent predictors of executive function and psychomotor tempo

Across the ACR-quartiles, for increasing ACR, there was a significant trend of increasing age, BMI, systolic blood pressure, current use of antihypertensive medication, current smoking, eGFR, IMT, Δ IMT, TPA and Δ TPA.

In multiple regression, higher ACR, higher Δ ACR and larger IMT were independently associated ($p = 0.016$, 0.002 and 0.010 , respectively) with lower DST score. Higher Δ ACR was associated ($p = 0.006$) with a lower FTT score. Higher Δ IMT had a borderline significant association ($p = 0.08$) with lower FTT score. Smoking was independently associated ($p < 0.001$) with lower DST and FTT scores. Higher BMI was independently associated ($p = 0.011$) with lower FTT score. Higher eGFR was independently associated ($p = 0.004$) with lower DST score.

In ANCOVA, there was a significant linear trend ($p = 0.003$) of a lower DST score for increasing ACR in women. In both genders, those with IMT at or above the median scored lower on DST than those with IMT below the median ($p = 0.031$ for women, $p = 0.017$ for men). Women with IMT at or above the median had a significant linear trend ($p = 0.006$) of a lower DST score for increasing ACR.

Paper III – Probable parental LOAD, the ApoE ϵ 4 allele, higher tHcy and higher eGFR are independently associated with smaller hippocampal volume, especially in women

In multiple regression, probable parental LOAD, presence of the ApoE ϵ 4 allele, higher tHcy and higher eGFR were independently associated ($p = 0.058, 0.015, 0.004$ and 0.045 , respectively) with smaller hippocampal volume.

Stratified by gender and using the most relevant variables – age, presence of the ApoE ϵ 4 allele, probable parental LOAD, tHcy, cobalamin, eGFR and folic acid – the associations strengthened in women and diminished in men.

In age and sex adjusted ANCOVA, hippocampal volume was significantly smaller and lateral ventricular volume significantly larger in cases with SMC and MCI compared to controls. In cases with MCI, the volumes of amygdala, cerebral cortex and cerebrum were significantly smaller than in controls. Cases with MCI had higher volume of white matter hyperintensities (WMH) than controls. MR volumetry of the hippocampus and the lateral ventricles distinguished subjects with SMC and MCI from controls.

In receiver operating curve analysis, MR volumetry did not distinguish well between controls and SMC, nor between controls and MCI. The area under the curve in SMC and MCI compared to controls was less than 0.68 for all volumes of cerebral structures.

In multiple regression analysis, higher tHcy was significantly associated with smaller volumes of hippocampus, amygdala, cerebral cortex and cerebrum and with larger lateral ventricles.

Higher total cholesterol was significantly associated with larger hippocampal, amygdalar and cerebral volumes, and with smaller lateral ventricular volume.

In the sample, 38.5 % of the participants were carriers of the ApoE ϵ 4 allele (2.0 % ϵ 2/ ϵ 4 heterozygotes, 4.0 % ϵ 4/ ϵ 4 homozygotes and 32.3 % ϵ 3/ ϵ 4 heterozygotes). Of controls, participants with SMC and MCI, 41 %, 52 % and 34 %, respectively, were carriers of the ApoE ϵ 4 allele.

Methodological discussion

Study designs

The Tromsø Dementia Study (papers I and III) is a cross-sectional nested case control study in Tromsø 6. Advantages of cross-sectional case control studies are that many exposures can be examined, and that associations between them and disease outcomes can be assessed. They are therefore hypothesis generating. However, they can not test causality.

Paper I had 161 participants, comprising 58 controls and 103 cases with MCI. Paper III had 198 participants, comprising 58 controls, 25 cases with SMC and 115 cases with MCI.

The small sample sizes entail that the chances of making statistical type 1 and type 2 errors are relatively high. A type 1 error is to reject a null hypothesis when it is true, and a type 2 error is failing to reject a null hypothesis when it is false [137].

Paper II is a prospective cohort study based on data from Tromsø 4 and Tromsø 6. Participants (1577 in total) were selected from the Tromsø Study cohort, and had participated in the second visits in both Tromsø 4 and Tromsø 6 [113]. Cohort studies seek associations between exposures and disease outcomes. They are, like cross-sectional case-control studies, hypothesis generating and can not test causality. Causal associations can, however, be expected if Bradford Hill criteria are sufficiently fulfilled. Due to the high number of participants, the chances were small of making type 1 and 2 errors.

Internal and external validity

Internal validity expresses whether the study results are valid for the population from which the study sample is drawn. External validity expresses whether the study results are also valid for other populations, such as the general population [137]. Internal validity is threatened by error and bias.

Error and bias

“Man approaches the unattainable truth through a succession of errors” (Aldous Huxley, 1894-1963). Errors, whether they be random or systematic, are common in science. Error and bias can occur in all stages of a research project [137]. Bias can be defined as a systematic error in the design or conduct of a study [138]. Bias is an error which affects one group more than another, and is therefore more important than random errors which affect comparison groups equally. Bias can distort associations and create non-existent associations. The amount of bias and error in a research project determines the internal validity of the results – to what extent they are valid for the population the study sample is drawn from. If the sample is representative of the population it is drawn from, and the study results are not erroneous or biased, then the results have internal validity. If this population is representative of the general population, then the results have external validity for the general population.

A common broad classification of error and bias divides this into selection bias, information bias and confounding. There are numerous kinds of bias, such as interpretation bias, where the investigator has a preferred outcome in mind and publication bias, where the investigator reports publishable findings.

Selection bias

Bias can result from the choice of study population. Volunteers tend to differ in many characteristics compared to non-volunteers, e.g. income and health status. Selection bias occurs when a systematic error in the ascertainment of study subjects results in a tendency that distorts the measure expressing the association between exposure and outcome [138].

In the Tromsø Dementia Study, persons with low cognitive test scores in the second Tromsø 6 visit, who also had answered “Yes” to the question “Has your memory declined” on the first Tromsø 6 visit questionnaire, were invited as cases. The questionnaire inclusion criterion was due to ethical concerns. A considerable proportion of persons with AD are unaware of their cognitive impairment [139]. It would therefore be unethical to diagnose a neurodegenerative disease for which there is no effective treatment, without permission. Persons without subjective memory complaints who answered “No” to the question “Has your memory declined” on the questionnaire, and with low cognitive test scores in the second Tromsø 6 visit, were therefore not invited to the Tromsø Dementia Study. They might differ in several aspects from the cases who attended.

The number of invited cases to the Tromsø Dementia Study was 403, 139 taking part. Cognitive impairment in invited cases might have contributed to the low participation. The invited cases who did not take part might differ from attendees in several aspects.

The number of invited controls was 180, 73 taking part. Of these, 15 were excluded from the study (figure 1, paper I). The invited controls who did not take part might differ from the attendees in several characteristics [137]. The low attendance rate in the Tromsø Dementia Study increases the likelihood of selection bias. For example, among the 58 controls in the Tromsø Dementia Study, 41 % were carriers of the ApoE ε4 allele. This is clearly more than expected in healthy controls. One explanation might be that persons with AD in their families were more willing to take part.

Four different cognitive tests were used to select cases with MCI. It was sufficient to score below the cutoff value on one test to be defined as a case. Table 1 in paper I shows how the cases in groups 2-4 in men and women differ with regard to which cognitive tests defined them as cases. The results of between-group comparisons might therefore be biased. It might have been better to select all cases with MCI in the same way.

In paper II, all participants were without self-reported stroke and macroalbuminuria and had measurements of ACR, IMT and TPA from both Tromsø 4 and Tromsø 6 and cognitive test scores from Tromsø 6. The Tromsø Study has had a high attendance rate, 82 % in Tromsø 2, 79 % in Tromsø 3, 75 % in Tromsø 4, 81 % in Tromsø 5 and 66 % (not so high) in Tromsø 6, and is well defined [113]. A cohort study with a participation rate above 80 % is considered more unlikely to produce a great

deal of selection bias [140]. Moreover, selection bias is less problematic in cohort studies as, at recruitment, the outcome of interest has yet to take place [140]. The high number of participants in paper II also reduces the likelihood of selection bias.

Papers I and III are therefore more prone to selection bias than paper II.

Information bias

Information bias can be described as bias in the collection, analysis and interpretation of data [137]. Misclassification was a central issue in the Tromsø Dementia Study (papers I and III). Cases were selected from the second Tromsø 6 visit because of low cognitive test scores. MCI was then appraised in the Tromsø Dementia Study based on Petersen's original construct [141]. Cases with cerebral pathology such as cerebral strokes (not lacunar) and tumors on MRI were excluded.

The resulting cases with MCI were considered to have probable prodromal sporadic LOAD, probable prodromal familial LOAD or to be intermediate. They might also have co-existing CSVD. However, cases could, for example, be in the prodromal stage of dementia with Lewy bodies, and not have MCI due to prodromal LOAD [142].

Persons with MCI have an increased risk of dementia, most often due to AD which is most prevalent. However, MCI is a heterogenous condition. The majority develop dementia, but some revert to normal cognitive function and do not necessarily have an increased risk for dementia [143]. The proportion of MCI cases in the Tromsø Dementia Study with prodromal LOAD or CSVD is therefore uncertain.

Existing biomarkers and cognitive tests can not adequately detect AD in preclinical and prodromal stages. There might therefore, for example, be controls with preclinical LOAD and preclinical dementia with Lewy bodies. In clinical studies and trials on MCI and AD, finding valid cases is challenging. PET amyloid imaging and CSF biomarkers are therefore applied to enrich samples [91,108]. This was not feasible in the Tromsø Dementia Study. However, the classification of cases into probable prodromal sporadic LOAD, probable prodromal familial LOAD and with or without parental LOAD, might function as enrichment in the latter groups.

Questionnaires from the first and second Tromsø 4 and Tromsø 6 visits gathered information on education, alcohol usage and cardiovascular risk factors such as smoking, hypertension, diabetes, coronary disease and stroke. This information was susceptible to recall bias. However, studies have shown that self-reporting of chronic diseases have high validity [144-146]. In a study on the validity of self-reported stroke in the Tromsø Study, Engstad et al. found that self-reported stroke had a high positive predictive value and concluded that questionnaires could be used in epidemiological

research to assess a history of stroke [147]. Studies have shown that self-reported alcohol consumption can identify high alcohol consumers with a relatively high sensitivity and specificity, and that self-reported smoking has high validity in adults [148,149].

A case control study should preferentially have more than one control for each case [150]. For logistical reasons, there were only 58 controls in the Tromsø Dementia Study, around half the number of cases. The low number of controls reduces the internal validity of the results in the Tromsø Dementia Study.

Cases in the Tromsø Dementia Study had MCI or SMC, and controls were considered cognitively healthy. Cases and controls may therefore have differed in their abilities to recall past exposures. Recall bias is a concern especially in case-control studies [138]. Cases and controls answered questionnaires regarding past exposures in Tromsø 6, and in the Tromsø Dementia Study provided information on past exposures in interviews. Errors in recall of past exposures can bias the results of a study.

The cases were, in paper I, classified into three groups. The classification was based on information on the dispersion of probable LOAD among biological relatives in their families obtained in interviews with cases and their companions (most often their spouses). Companions had been invited for verification and for collateral information, as information from persons with MCI might be unreliable. However, family memories usually diminish late in the course of AD. Nevertheless, there was a risk for misclassification due to erroneous information.

In paper III, the cases with SMC could have been misclassified as they lacked MMSE scores from Tromsø 6. However, their mean MMSE score in the Tromsø Dementia Study was 0.8 points higher than cases with MCI and 1.2 points lower than controls. Moreover, SMC represents a more heterogeneous condition than MCI, and can for example stem from anxiety and depression [55].

NeuroQuant has been validated by comparisons with manually segmented volumetric measurements, and can detect differences in brain volumes between cognitively healthy older adults and persons with MCI [151,152]. NeuroQuant has also been shown to distinguish AD from non-dementia in clinical practice [153]. Errors in NeuroQuant measurements are probably random and of limited impact.

In paper II, ACR was calculated for all 1 577 participants by measuring urine albumin concentration and urine creatinine. Ultrasonography of the right internal carotid artery rendered measurements of IMT and TPA for all 1 577 participants. Errors in ACR, IMT and TPA measurements are probably

random and reduce the chances of finding significant associations, i.e. increase the chance of not rejecting a false null hypothesis.

Confounding

Confounding refers to a situation in which a non-causal association between a given exposure and an outcome is observed as a result of the influence of a third variable, which is designated a confounder. The confounder must be related to both the putative risk factor and the outcome. The confounder is responsible for all or part of the statistical association between the exposure and the outcome [138]. A confounder is an extraneous variable whose presence affects the variables being studied, so that the results do not reflect the actual relationship between the variables under study [154].

In papers I-III, age is the most important confounder, as it is associated both with many exposure variables and with all outcome variables. To control for confounding, the participants were drawn from the same population. Moreover, in multiple regression, the analyses were adjusted for several other variables than the main exposure variables, to better estimate the associations of main interest. For example, in addition to major confounders such as age and sex, analyses were adjusted for education, smoking, alcohol intake, folic acid, cobalamin and eGFR. However, there might still be residual confounding not accounted for due to unknown confounders.

In papers I and III (Tromsø Dementia Study), eligible controls were matched for sex and age. However, inadequate matching for age resulted in case groups that were significantly older than controls. In paper I, this applied to men in groups 2 and 3 and in paper III to the MCI group.

Interaction differs from confounding. Interaction occurs when the effect of one exposure variable for an outcome depends on the level of one or more other exposure variables. The effect of one exposure becomes changed or modified, dependent on the level of another exposure. Interaction is therefore also known as effect modification [155]. To test for interactions, interaction terms (products of two exposures) were applied in the ANCOVA and multiple regression analyses. In paper I, there was an interaction between gender and groups 1-4 for tHcy. All analyses were therefore performed gender specific. In paper III, there was a borderline significant interaction between gender and probable parental LOAD for hippocampal volume. Additional multiple regression analysis stratified by gender and parental LOAD was therefore performed.

External validity of the results in papers I-III

External validity pertains to whether the results can be generalized. The data in papers I-III are selected from samples drawn from the Tromsø Study. If our study samples are representative of the

Tromsø 6 cohort, and the results have internal validity, then our study results might have external validity and apply beyond the Tromsø 6 cohort.

In papers I and III, analyses were performed on small numbers of participants, and the number of controls was less than half the number of cases. This increases the probability of finding false associations, both positive and negative, and renders it uncertain whether the study samples are representative of the Tromsø 6 cohort. The probability that the results have internal and external validity is therefore lower.

Paper II has many participants from a well defined population and, as it is not a case-control study, the probability of achieving internal and external validity is higher.

Discussion of results

Paper I

In this cross sectional case-control study, ANCOVA was gender stratified as there was an interaction between gender and groups 1-4 for tHcy.

In the original case group classification, group 4 represented probable prodromal familial LOAD, group 2 represented probable prodromal sporadic LOAD and group 3 represented an intermediate group.

Unlike the other case groups, women with probable prodromal familial LOAD did not have significantly higher tHcy than controls. In men, all case groups had significantly higher tHcy than controls. Unlike men, women with probable prodromal LOAD differed significantly in the volumes of cerebral structures compared with controls and other case groups.

Earlier studies and trials on tHcy and AD have shown equivocal results. For over 20 years it has been debated whether tHcy is a risk marker or a risk factor for AD [67]. Recently, an international expert group concluded in a consensus statement that elevated tHcy is a modifiable risk factor for development of cognitive decline, dementia, and AD in older persons [67]. tHcy appears to be a risk factor both for AD and CSVD [22]. Our results might help explain equivocal results in earlier studies on tHcy and risk of LOAD [67,156,157].

Women with probable prodromal familial LOAD did not have significantly higher tHcy than controls, including in the alternative classification of group 4, unlike the other case groups. Moreover, in the alternative classification, the differences in volumes of cerebral structures between women in group 4 and women in groups 1-3 increased. Women with probable prodromal familial LOAD in particular

differed in hippocampal volume. Their mean hippocampal volume was smaller than in controls, in women with probable prodromal sporadic LOAD and in women in the intermediate group. Women with probable prodromal familial LOAD also differed in the volume of lateral ventricles. They had larger lateral ventricular volume than controls and women with probable prodromal sporadic LOAD.

Ventricular enlargement is a convenient measure of disease progression, due to the high contrast between CSF and the surrounding brain tissue [99]. In a prospective study from 2008, Nestor et al. found that at baseline, ventricular volume was significantly larger in both AD subjects and MCI subjects compared to controls [97]. After six months, all groups had a significant increase in ventricular volume. The AD subjects had a significantly greater ventricular enlargement than both subjects with MCI and controls. Subjects with MCI also had a significantly greater rate of enlargement than controls. In contrast to our study, Nestor et al. measured the volumes of all four cerebral ventricles, did not classify MCI into probable prodromal sporadic and familial LOAD, and did not perform gender specific analyses.

The gender difference in volumetry of cerebral structures in our study is consistent with earlier studies, which have shown gender differences [158]. Examples include a study of paternal and maternal transmission of familial LOAD, and a prospective study of AD and amnesic MCI [159-161]. It has been shown that the risk conferred for AD by being a first-degree relative of persons with AD, female or by having an $\epsilon 4$ allele is of similar magnitude [73]. Moreover, that having a first-degree family history of LOAD, especially when a parent is affected, is the most significant risk factor for developing LOAD [72]. Our volumetric findings particularly in women with MCI and probable parental LOAD, are consistent with this.

The differences in cerebral volumetric findings between women with probable prodromal sporadic LOAD and women with probable prodromal familial LOAD suggest that sporadic and familial LOAD might differ in etiology and pathophysiology [4,7,72,73]. The different findings in women and men in the cerebral volumetry of cases with probable prodromal familial LOAD compared to controls and cases with probable prodromal sporadic LOAD, suggest that familial LOAD might have gender differences.

In both genders in our sample, more than 65 % of the biological relatives with probable LOAD were women. This is similar to previous studies which suggest that maternal transmission of AD is more frequent than paternal transmission, and that having an AD-affected mother confers a greater risk than having an AD-affected father [162-164]. Likewise, Berti et al. found grey matter volume reductions in normal individuals with a maternal history of AD study, but not in normal individuals

with a paternal history of AD [159]. They concluded that maternal transmission might lead to a more increased risk for LOAD than paternal transmission.

In a prospective study, Honea et al. found progressive regional atrophy, including of the medial temporal lobes, in cognitive normal adults with a maternal history of AD [161]. Among controls in our study, five female controls had mothers with probable LOAD and eight male controls had mothers with probable LOAD. Compared with the number of male and female controls, this constitutes an equal distribution of mothers with probable LOAD among male and female controls. If female controls had smaller hippocampus because of this, it would have become more difficult to distinguish cases from controls. However, this might be an explanation for not finding differences between male controls and cases.

Many studies have found sex differences in AD. In 2015, the American Alzheimer's Association convened experts to explore these differences [165,166]. They moved forward a research agenda to better understand the biological underpinnings of sex and gender related disparities of risk for AD. One of the areas they identified in which increased research was needed was the role of sex chromosomes on AD-like biological changes, using genome wide association studies (GWAS) and other techniques to more fully analyze the X and Y chromosomes.

In a review from 2014 on sex and gender differences in AD, Mielke et al. concluded that prevalence and incidence of AD, brain structure and function and risk factors vary by sex and gender [167]. In future research on AD, they recommended carrying out sex and gender specific studies and trials.

In a prospective study from 2015, Lin et al. found marked gender differences in progression of mild cognitive impairment over 8 years [168]. In MCI subjects, women declined at much higher rates than men. Consequently, they recommended gender specific research in AD.

In a prospective study from 2010 on elderly subjects with MCI and AD and cognitively healthy controls, Hua et al. found significant age and sex differences in atrophic rates [169]. Brain atrophic rates were about 1 %-1.5 % faster in women than men. Atrophy was faster in younger than older subjects, and most prominently in mild cognitive impairment.

In a prospective study from 2013 that measured the effects of age, ApoE ϵ 4 and sex on brain atrophy, Holland et al. found that sex differences in atrophy rates were as large as differences associated with ApoE ϵ 4 [170]. The study population consisted of cognitively healthy elderly, elderly with MCI and elderly with AD. In all stages, from healthy aging through AD, women had higher rates of brain atrophy than men, and the magnitude of the sex differences was at least as large as the magnitude of the ApoE ϵ 4 effects.

In our study population, the distribution of ApoE genotypes were as follows: $\epsilon 2/\epsilon 2$ 0.6 %, $\epsilon 2/\epsilon 3$ 11.2 %, $\epsilon 2/\epsilon 4$ 1.9 %, $\epsilon 3/\epsilon 3$ 50.9 %, $\epsilon 3/\epsilon 4$ 30.4 % and $\epsilon 4/\epsilon 4$ 5.0 %. The ApoE $\epsilon 4$ allele was prevalent, 37.3 % of participants being carriers of the ApoE $\epsilon 4$ allele. Among cases and controls, 35 % and 41 % had the ApoE $\epsilon 4$ allele, respectively.

A Norwegian study from 2008 by Sando et al. found that among elderly persons with probable LOAD, the ApoE $\epsilon 4$ allele was present in 64.1 % of cases [77].

In women, group 2 (probable prodromal sporadic LOAD) had the lowest prevalence at 27 %. In men, group 3 (the intermediate group) had the lowest prevalence at 17 %. Prevalence in the other groups ranged from 33 % to 46 %. In women, the difference was largest between the groups for probable prodromal familial LOAD and probable prodromal sporadic LOAD. In the former group, 47 % had the ApoE $\epsilon 4$ allele, while 27 % of the latter group had the ApoE $\epsilon 4$ allele. This might explain why women with probable prodromal familial LOAD differed most in volumetry of cerebral structures in our study.

Previous studies have shown associations between the ApoE $\epsilon 4$ allele and size of cerebral structures, also in cognitive intact adults [171-174]. A recent prospective study by Altmann et al. found that female carriers of the ApoE $\epsilon 4$ allele had a higher risk than male carriers of converting from healthy cognitive function to MCI, and from MCI to AD [175]. However, in our cross-sectional study, although the alternative classification led to enhanced differences in group 4 in women, the prevalence of the ApoE $\epsilon 4$ allele fell from 47 % to 38 %. Thus, the differences in group 4 can not be fully attributed to the prevalence of the ApoE $\epsilon 4$ allele.

In both male and female control groups, many were carriers of the ApoE $\epsilon 4$ allele and many had parents with probable LOAD. In AD, presence of the ApoE $\epsilon 4$ allele is associated with increased rates of hippocampal loss [176]. It is conceived that MRI changes due to AD precede the onset of MCI [8]. As probable parental LOAD and the ApoE $\epsilon 4$ allele were prevalent, several controls might have preclinical LOAD. This would render it harder to find differences between cases and controls. As such, it strengthens our findings.

The Norwegian study from 2008 by Sando et al. found that 26.4 % of cognitively normal elders were carriers of the ApoE $\epsilon 4$ allele [77]. Among our controls, 41 % were carriers of the ApoE $\epsilon 4$ allele. The reason for the high prevalence of the ApoE $\epsilon 4$ allele among our controls is unclear. One possible explanation is that invited controls who had biological relatives with LOAD were especially eager to attend the Tromsø Dementia Study.

There is insufficient knowledge on the prevalence of the ApoE ϵ 4 allele among cognitive healthy adults and among adults with AD in Norway and other countries [77]. The ApoE ϵ 4 allele and the ApoE ϵ 3 allele are inversely correlated in Europe, with the ApoE ϵ 4 allele being more prevalent in populations in Northern Europe than in Southern Europe [177]. The ApoE ϵ 4 allele prevalence varies among AD patients by region and within each country, with the highest prevalence in northern Europe and the lowest in Asia and Southern Europe [178].

With the exception of tHcy, we found no differences in cardiovascular risk factors between groups. This is in line with earlier cross-sectional studies that have found no significant impact of cardiovascular risk factors on the risk of LOAD [156,179].

Paper II

In multivariate linear regression, ACR and IMT measured in 1994 independently predicted processing speed (DST) in 2007. To our knowledge, there have been no previous prospective studies on cognitive function that apply internal carotid IMT and albuminuria as exposure variables simultaneously and therefore no studies which have shown that albuminuria and carotid IMT independently predict cognitive function.

Higher Δ ACR was associated with lower processing speed and psychomotor tempo (FTT), while higher Δ IMT had a borderline association with lower psychomotor tempo. Substitution of IMT and Δ IMT with TPA and Δ TPA yielded the same associations, except that higher Δ TPA independently was significantly associated with both lower processing speed and psychomotor tempo.

These associations were for ACR levels substantially below the limits for microalbuminuria. This suggests that low-grade albuminuria has relevance for cognitive function. Earlier studies have shown that ACR levels below the usually defined cut-off levels for pathological albuminuria have independently predicted mortality [180].

Small vessel disease is considered a systemic disorder. Microalbuminuria might therefore reflect endothelial dysfunction in the cerebral microcirculation due to CSVD [181]. The brain and kidneys share hemodynamic properties, including low resistance and high circulatory flow [84]. A systematic review and meta-analysis from 2017 by Georgakis et al. found that albuminuria was independently associated with cognitive impairment, dementia and cognitive decline [84]. It also showed that albuminuria was associated with diffuse neuropsychological defects similar to the profile of vascular cognitive impairment, the greatest impairment being in the domain of processing speed [182]. Paper II was included as one of 32 eligible studies in this systematic review and meta-analysis.

Georgakis et al. found, in another recent systematic review and meta-analysis, that albuminuria was independently associated with CSVD, as measured on MRI by WMH, lacunar infarcts, cerebral microbleeds and enlarged perivascular spaces [183]. These associations between microalbuminuria and CSVD lend support to the associations between microalbuminuria and cognitive function.

Our results are in line with the findings on cognitive aging by Baudoin et al. [184]. They found that the DST combined executive processes and perceptual speed, that executive functions are a significant mediator of age-related differences in memory, DST performance being the best predictor. Our results suggest that endothelial dysfunction and atherosclerosis independently contribute to the impairment in several cognitive domains that is associated with normal aging [185]. Also, our results add weight to studies which have shown that impaired executive function is present in early stages of VCI and VaD caused by CSVD [86,186].

Higher carotid IMT and TPA are risk factors for stroke and subsequent cognitive impairment [89]. Studies suggest that subclinical carotid atherosclerosis without stroke may also be an independent risk factor for cognitive decline and dementia [89]. However, study results have been equivocal, and it has not been ascertained that higher IMT and TPA are predictors of cognitive impairment [89,187,188]. In a recent cross-sectional study, Wang et al. found an association between carotid IMT and cognitive function measured with the MMSE, among stroke free middle-aged and older adults in a Chinese population [189]. In a prospective study, Zhong et al. assessed the impact of carotid atherosclerosis on 10-year changes in cognitive function [190]. Higher IMT was associated with an increased risk of cognitive impairment. However, higher IMT was not associated with lower DST scores 10 years later.

In ANCOVA, women with IMT at or above the median had a significant linear trend of a lower DST score for increasing ACR. Also, women with IMT below the median in the highest ACR quartile (ACR quartile 4) had significantly lower DST scores than corresponding women in the lower ACR quartiles (ACR quartiles 1-3). The reasons for these findings are unclear. One explanation might be that there is a closer connection between endothelial dysfunction and atherosclerosis in women than in men.

In our study, smoking independently predicted lower DST and FTT scores. Earlier prospective studies have also shown an association between smoking and cognitive impairment [191]. In a recent prospective study, Sabia et al. showed that, compared with never smokers, middle-aged male smokers experienced faster cognitive decline especially in executive function, but also in global cognition [192]. One reason for the gender difference in the study by Sabia et al., might be that male smokers smoked significantly more than female smokers. Our study results open up the possibility that smoking impairs motor speed, psychomotor speed and executive function independent of

endothelial dysfunction and atherosclerosis. To our knowledge, it has not been shown previously that albuminuria, internal carotid atherosclerosis and smoking independently predict psychomotor and executive function.

Previous studies have found equivocal associations between eGFR and cognitive function among persons from a general population [88,193,194]. In our study, higher eGFR was independently associated with lower DST score. One possible reason is that in our sample, which is from a general population, the mean eGFR was normal and had a very small standard deviation, and that the effect size (β value) in the multiple regression analysis was close to zero. Moreover, estimations of GFR creatinine-based equations do not perfectly reflect true GFR, especially when GFR is normal or near-normal.

Paper III

Volumes of hippocampus and cerebral structures served as surrogate markers for AD. However, other neurodegenerative diseases, CSVD and aging also lead to atrophy of hippocampus and other cerebral structures [195]. Exposure variables were cardiovascular and genetic risk factors.

One aim was to assess whether the fully automated software NeuroQuant could distinguish sufficiently between cognitive healthy controls on the one side and subjects with SMC or MCI on the other, to be useful in the clinical routine.

In a previous Norwegian study from a memory clinic, fully automated volumetry using NeuroQuant distinguished AD from MCI and subjective cognitive impairment, but did not distinguish between different kinds of dementia [104]. Receiver operating characteristic analyses were performed. The calculated area under the curve in AD compared to MCI and subjective cognitive impairment was 0.80 for hippocampus and 0.73 for the lateral ventricles. They concluded that NeuroQuant provided support for the results of other clinical investigations, but could not be used alone to distinguish between persons with AD and persons without dementia.

In a recent study on the same population by Persson et al., NeuroQuant was compared to visual evaluation of medial temporal lobe atrophy using the Scheltens scale [105]. They found that NeuroQuant and visual evaluation of medial temporal lobe atrophy correlated well, and had equivalent discriminatory power and accuracy in distinguishing AD patients from MCI and subjective cognitive impairment patients.

In our study using cognitive healthy controls, the calculated area under the curve in SMC and MCI compared to controls was less than 0.68 for all measured volumes of intracranial structures. Accordingly, our results imply that NeuroQuant is not useful in clinical practice to distinguish

between cognitive healthy persons and persons with MCI or SMC. Nevertheless, in the clinical routine, fully automated volumetry can be repeated to assess whether the atrophy rate is abnormal, and be useful with other biomarkers in diagnosing preclinical LOAD [151,196-198].

In a recent study by Tanpitukpongse et al., receiver operating characteristic curves assessed the prognostic efficacy of NeuroQuant and another fully automated software package, NeuroReader, to predict conversion of MCI to AD [199]. They found that hippocampal volume was the best single predictor of conversion of MCI to AD.

This is consistent with our findings in the Tromsø Dementia Study (papers I and III). We found that the most significant differences between groups were for hippocampal volume, and that exposure variables of interest particularly had associations with hippocampal volume. Hippocampal atrophy is an early finding in AD, and as our cases had SMC and MCI, associations with hippocampal volume were most likely [99,200].

In ANCOVA, MR volumetry distinguished persons with SMC and MCI from controls. The MCI group was, however, significantly older than controls, which can not be fully adjusted for in linear regression analysis. However, the SMC group was not significantly older than controls, but differed significantly from controls in volumetric measurements. This increases the probability that the MCI group also differed significantly from controls. Volumetry of the hippocampus and the lateral ventricles in particular distinguished the SMC and MCI groups from controls.

Compared to controls, the volumes of the cerebral cortex and cerebrum were smaller in the MCI group. In contrast to the medial temporal lobe, recognizable atrophy of these structures occurs later in the disease course of AD [171]. However, the MCI group was significantly older than controls and the validity of these findings is therefore uncertain.

Amygdala atrophy is also an early finding in AD. Findings have, however, been less consistent than for hippocampal atrophy [201]. In two large, independent samples of very mild and mild AD patients, Poulin et al. found that amygdala atrophy was comparable to hippocampal atrophy using fully automated volumetry with the software package Freesurfer [201].

In our sample, amygdala was smaller only in persons with MCI. This is in line with inconsistent findings in previous studies. A reason might be that the boundaries of hippocampus are easier to recognize both visually and with fully automated software [99]. The MCI group was significantly older than the control group and the validity of this finding is therefore uncertain. This also applies to the volume of white matter hyperintensities (WMH) which in our study was larger only in the MCI group.

WMH are considered the most common marker of small vessel disease in the brain, and are associated with an increased risk of developing AD [202,203]. However, studies on the clinical significance of WMH in patients with MCI and AD have reported mixed results [202].

Associations between cardiovascular and genetic risk factors on the one hand, and volumes of cerebral structures on the other were tested in multiple regression analysis of all participants. tHcy was the risk factor with most associations with volumes of cerebral structures. Higher tHcy was associated with less hippocampal volume, less amygdalar volume, less volume of cerebral cortex, less cerebral volume and larger lateral ventricular volume.

Higher tHcy level has been associated with brain atrophy in several studies [204-206]. Elevated tHcy is associated with hippocampal atrophy in cognitively normal elderly people and with faster rates of medial temporal lobe atrophy in AD [207]. B-vitamin treatment in persons with high tHcy has been shown to reduce cerebral atrophy in gray matter regions specifically vulnerable to AD [206].

In multiple regression analysis, probable parental LOAD, presence of the ApoE ϵ 4 allele, lower total cholesterol, higher tHcy and higher eGFR were independently associated with smaller hippocampal volume. Stratified by gender, the associations were still significant in women, but not in men. In women, the association between probable parental LOAD and hippocampal volume became more significant. The reasons behind these independent associations are unclear. One explanation might be that sporadic and familial LOAD have different etiologies [41]. Another explanation is that these associations are spurious due to the low number of cases and controls. The difference between men and women may be due to sex differences in the etiology and pathophysiology of LOAD [167,208]. Our results might also suggest a difference between men and women with probable parental LOAD in acquiring LOAD, and underline the importance of performing sex-specific analyses in studies on LOAD [75].

Okonkwo et al. carried out a prospective study of cognitively healthy middle-aged adults who had one or two parents with LOAD. Over a 4-year interval, these cognitively healthy middle-aged (mean age at baseline was 54 years) adults exhibited significant atrophy in the posterior hippocampi in the absence of measurable cognitive changes [209]. This was regardless of maternal or paternal AD, and suggests that cerebral atrophy in AD starts earlier than presumed.

Lampert et al. carried out a prospective study on elder (mean age 80 years) subjects with MCI, who either had a parent or sibling with AD, or did not have a family history of AD [210]. Subjects with a family history of AD had greater atrophy of the amygdala, hippocampus and cortical gray matter compared to subjects without a family history of AD. However, when the ApoE ϵ 4 allele was added as a covariate, the family history effects of AD were no longer significant.

This differs from our findings. One explanation might be that Lampert et al., in contrast to Okongwo et al. and ourselves, mixed together cases with parental AD and cases with AD in a sibling. Parental LOAD represents a greater risk for LOAD than LOAD in a sibling [73]. Another explanation is that the participants in the study by Lampert et al. were considerably older than the participants in the study by Okongwo et al. and in our study. Okongwo et al. found no significant main effects of being a carrier of the ApoE ϵ 4 allele in their prospective study.

Higher total cholesterol was in our study independently associated with larger volumes of hippocampus, amygdala and cerebrum and smaller volumes of the lateral ventricles. We have no clear explanation for these associations, which could be spurious.

Cholesterol is a lipid that is essential for cell membrane structure and function [211]. The ApoE ϵ 4 allele confers the greatest risk for developing familial and sporadic LOAD, most likely by reducing cholesterol efflux from neuronal cells and astrocytes, and by binding and depositing A β [212]. Cholesterol metabolism and trafficking might thus be important for LOAD susceptibility. ApoE is essential for normal lipid homeostasis in the brain, and ApoE ϵ 4 is less efficient than ApoE ϵ 3 in delivering cholesterol to neurons [18,213].

Cholesterol might be a risk factor for both cardiovascular disease and AD. Studies and trials on cholesterol and AD have, however, rendered equivocal results [214,215]. High total cholesterol level at midlife has been associated with an increased risk of developing AD. Conversely, a high total cholesterol level between age 70 and 79 years has been found to reduce the risk of developing dementia between age 79 and 88 years.

In a cross-sectional study of participants free of stroke and cognitive impairment, and aged \geq 60 years, Qiu et al. found that high total cholesterol and diabetes were significantly or marginally associated with smaller hippocampus and entorhinal cortex in men [216].

Previous studies have shown that the presence of the ApoE ϵ 4 allele is associated with hippocampal atrophy, amygdalar atrophy, entorhinal cortex atrophy, increased brain atrophy and increased WMH volumes [217-219]. In our sample, we only found an association between the ApoE ϵ 4 allele and smaller hippocampal volume. The reason for this is probably that our study was of SMC and MCI, and the likelihood for finding atrophy of cerebral structures occurring later in the disease course of AD was less.

In our sample, higher eGFR was associated with smaller volumes of hippocampus, cerebrum and cerebral cortex [220]. We have no explanations for these associations which could be spurious.

In a recent study on a cognitively normal population, Cho et al. found no associations between eGFR and cerebral cortical atrophy [221]. In a review and meta-analysis by Derckers et al. on dementia risk

in renal dysfunction, they found no clear association between eGFR levels and cognitive decline or dementia risk [220].

In our sample, the ApoE ϵ 4 allele was present in 41 % of controls, 52 % of cases with SMC and 34 % of cases with MCI. The prevalence of the ApoE ϵ 4 allele in the general population is approximately 15 % and approximately 40 % in patients with AD [212]. However, these estimates vary, also with latitude. Another estimate is that approximately 65-75 % of patients with AD carry the ϵ 4 allele [222]. The APOE allele distribution seems to depend on ethnicity and varies with latitude, higher ϵ 4 frequencies being more common close to the equator and in the northern polar region.

In a Norwegian study by Sando et al. of 376 AD patients and 561 healthy controls, 26.4 % of the controls and 64.1 % of the AD patients were carriers of the ApoE ϵ 4 allele [77].

A reason for the high prevalence in our control group might be that among invited controls, persons with LOAD in their family consented more readily. The same reason may also apply to the even higher prevalence in the SMC group, and increases the probability that cases in the SMC group had prodromal LOAD.

Conclusions and implications

Paper I

In contrast to women and men with probable prodromal sporadic LOAD, and men with probable prodromal familial LOAD, women with probable prodromal familial LOAD did not have significantly elevated tHcy compared to controls.

Furthermore, women with MCI and probable prodromal familial LOAD differed significantly from controls and from women with probable prodromal sporadic LOAD in fully automated volumetry of hippocampus and lateral ventricles. Similar differences were not found in men.

Previous studies have found gender differences in volumes of cerebral structures in cognitive impairment. However, to our knowledge, previous studies have not shown the results just mentioned.

The implications of our findings are unclear, and open up for many explanations. For example that sporadic LOAD and familial LOAD have different etiologies and pathophysiologies, that women have a higher risk of inheriting AD and that tHcy is not a risk factor for familial LOAD in women.

To our knowledge, previous studies on MCI, prodromal AD and MR volumetry have not distinguished between probable prodromal sporadic LOAD and probable prodromal familial LOAD. By doing so, we could look for differences between them. Our results suggest that making this distinction is relevant.

Similar studies should be carried out to check the validity of our results. These studies should have a markedly larger sample size (both controls and cases) to achieve higher statistical power.

Preferably, PET amyloid imaging, quantification of A β 42, p-tau and t-tau in CSF should be applied for enrichment of cases.

If our results are replicated, their validity is increased. Further research is then warranted to clarify implications.

Paper II

Our findings suggest that low-grade albuminuria, carotid atherosclerosis and smoking independently predicts impaired psychomotor tempo and executive function in a general population.

To our knowledge, it has not previously been shown that these risk factors are independently associated with cognitive function.

Our findings are consistent with previous studies that have shown associations between albuminuria, smoking and carotid atherosclerosis on the one hand, but not for all independently, and cognitive function on the other.

Further studies should be carried out to elucidate the associations between albuminuria and carotid atherosclerosis on the one side, and cognitive function on the other. For example, to assess whether these also reflect normal cognitive aging due to an aging cerebral vasculature.

Paper III

Our main finding was that probable parental LOAD, the Apo ϵ 4 allele, higher tHcy and higher eGFR were independently associated with smaller hippocampal volume. This finding was particularly for women. To our knowledge, this has not been shown in earlier studies.

Our findings suggest that research on AD should differentiate between sporadic LOAD and familial LOAD, and also between genders, to find underlying disease mechanisms and etiologies.

Similar studies with more participants should be carried out to see whether our findings are replicated. PET amyloid imaging and quantification of A β 42, p-tau and t-tau in CSF should preferably be applied for enrichment of cases.

If our findings are replicated, further studies should be carried out to clarify implications.

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Tromsø-undersøkelsen

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

2007 – 2008 KONFIDENSIELT

HELSE OG SYKDOMMER

1 Hvordan vurderer du din egen helse sånn i alminnelighet?

- Meget god
- God
- Verken god eller dårlig
- Dårlig
- Meget dårlig

+

2 Hvordan synes du at helsen din er sammenlignet med andre på din alder?

- Mye bedre
- Litt bedre
- Omtrent lik
- Litt dårligere
- Mye dårligere

3 Har du eller har du hatt?

	Ja	Nei	Alder første gang	
Hjerteinfarkt.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Angina pectoris (hjertekrampe).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Hjerneslag/hjerneblødning.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Hjerteflimmer (atrieflimmer).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Høyt blodtrykk.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Beinskjørhet (osteoporose).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Astma.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Kronisk bronkitt/emfysem/KOLS.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Diabetes.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Psykiske plager (som du har søkt hjelp for).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Lavt stoffskifte.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Nyresykdom, unntatt urinveisinfeksjon.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>
Migrene.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>

4 Har du langvarige eller stadig tilbakevendende smerter som har vart i 3 måneder eller mer?

- Ja Nei

5 Hvor ofte har du vært plaget av søvnløshet de siste 12 måneder?

- Aldri, eller noen få ganger
- 1-3 ganger i måneden
- Omtrent 1 gang i uken
- Mer enn 1 gang i uken

+

6 Under finner du en liste over ulike problemer. Har du opplevd noe av dette den siste uken (til og med i dag)? (Sett ett kryss for hver plage)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Føler deg redd eller engstelig.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Matthet eller svimmelhet.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Føler deg anspent eller oppjaget.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lett for å klandre deg selv....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Søvnproblemer.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nedtrykt, tungsindig.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Følelse av å være unyttig, lite verd.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Følelse av at alt er et slit.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Følelse av håpløshet mht. framtida.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

BRUK AV HELSETJENESTER

7 Har du i løpet av de siste 12 måneder vært hos: Hvis JA; Hvor mange ganger?

	Ja	Nei	Ant ggr
Fastlege/allmennlege.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Psykiater/psykolog.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Legespesialist utenfor sykehus (utenom fastlege/allmennlege/psykiater).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Fysioterapeut.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Kiropraktor.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Annen behandler (homøopat, akupunktør, fotsoneterapeut, naturmedisiner, håndspålegger, healer, synsk el.l).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Tannlege/tannpleier.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

8 Har du i løpet av de siste 12 måneder vært på sykehus?

	Ja	Nei	Ant ggr
Innlagt på sykehus.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Konsultasjon ved sykehus uten innleggelse;			
Ved psykiatrisk poliklinikk.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Ved annen sykehuspoliklinikk.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

9 Har du gjennomgått noen form for operasjon i løpet av de siste 3 årene?

- Ja Nei

+

BRUK AV MEDISINER

- 10 Bruker du, eller har du brukt, noen av følgende medisiner? (Sett ett kryss for hver linje)

+	Aldri brukt			Alder første gang
	Nå	Før		
Medisin mot høyt blodtrykk...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Kolesterolsenkende medisin...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Medisin mot hjertesykdom...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Vann drivende medisin.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Medisin mot beinskjørhet (osteoporose).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Insulin.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Diabetesmedisin (tabletter).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Stoffskiftemedisinene Thyroxin/levaxin.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

- 11 Hvor ofte har du i løpet av de siste 4 ukene brukt følgende medisiner? (Sett ett kryss pr linje)

	Ikke brukt siste 4 uker	Sjeldnere enn hver uke	Hver uke, men ikke daglig	Daglig
Smertestillende på resept.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Smertestillende uten resept.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sovemidler.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Beroligende medisiner.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Medisin mot depresjon.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 12 Skriv ned alle medisiner – både de med og uten resept – som du har brukt regelmessig i siste 4 ukers periode. (Ikke regn med vitaminer, mineraler, urter, naturmedisin, andre kosttilskudd etc.)

Får du ikke plass til alle medisiner, bruk eget ark.

VED FRAMMØTE vil du bli spurt om du har brukt antibiotika eller smertestillende medisiner de siste 24 timene. Om du har det, vil vi be om at du oppgir preparat, styrke, dose og tidspunkt

FAMILIE OG VENNER

- 13 Hvem bor du sammen med? (Sett kryss for hvert spørsmål og angi antall)

	+	Ja	Nei	Antall
Ektefelle/samboer.....	<input type="checkbox"/>	<input type="checkbox"/>		<input type="text"/>
Andre personer over 18 år.....	<input type="checkbox"/>	<input type="checkbox"/>		<input type="text"/>
Personer under 18 år.....	<input type="checkbox"/>	<input type="checkbox"/>		<input type="text"/>

- 14 Kryss av for de slektninger som har eller har hatt

	Foreldre	Barn	Søsken
Hjerteinfarkt.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hjerteinfarkt før fylte 60 år.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Angina pectoris (hjertekrampe).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hjerneslag/hjerneblødning.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Beinskjørhet (osteoporose).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Magesår/tolvfingertarmsår.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Astma.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diabetes.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Demens.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Psysiske plager.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Rusproblemer.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 15 Har du nok venner som kan gi deg hjelp når du trenger det?

Ja Nei

- 16 Har du nok venner som du kan snakke fortrolig med?

Ja Nei

- 17 Hvor ofte tar du vanligvis del i foreningsvirksomhet som for eksempel syklubb, idrettslag, politiske lag, religiøse eller andre foreninger?

- Aldri, eller noen få ganger i året
 1-2 ganger i måneden
 Omtrent 1 gang i uken
 Mer enn en gang i uken

ARBEID, TRYGD OG INNTEKT

- 18 Hva er din høyeste fullførte utdanning? (Sett ett kryss)

- Grunnskole, framhaldsskole eller folkehøyskole
 Yrkesfaglig videregående, yrkesskole eller realskole
 Allmennfaglig videregående skole eller gymnas
 Høyskole eller universitet, mindre enn 4 år
 Høyskole eller universitet, 4 år eller mer

- 19 Hva er din hovedaktivitet? (Sett ett kryss)

- Yrkesaktiv heltid Hjemmевærende
 Yrkesaktiv deltid Pensjonist/trygdet
 Arbeidsledig Student/militærtjeneste

- 20 **Mottar du noen av følgende ytelser?**
- Alderstrygd, førtidspensjon (AFP) eller etterlattepensjon
 - Sykepenger (er sykemeldt)
 - Rehabiliterings-/attføringspenger
 - Uføreytelse/pensjon, hel +
 - Uføreytelse/pensjon, delvis
 - Dagpenger under arbeidsledighet
 - Overgangstønad
 - Sosialhjelp/-stønad

- 21 **Hvor høy var husholdningens samlede bruttoinntekt siste år?** Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende.
- | | |
|---|--|
| <input type="checkbox"/> Under 125 000 kr | <input type="checkbox"/> 401 000-550 000 kr |
| <input type="checkbox"/> 125 000-200 000 kr | <input type="checkbox"/> 551 000-700 000 kr |
| <input type="checkbox"/> 201 000-300 000 kr | <input type="checkbox"/> 701 000 -850 000 kr |
| <input type="checkbox"/> 301 000-400 000 kr | <input type="checkbox"/> Over 850 000 kr |

- 22 **Arbeider du utendørs minst 25 % av tiden, eller i lokaler med lav temperatur, som for eksempel lager-/industrihaller?**
- Ja Nei

FYSISK AKTIVITET

- 23 **Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt?**
- For det meste stillesittende arbeid
(f.eks. skrivebordsarbeid, montering)
 - Arbeid som krever at du går mye
(f.eks. ekspeditørarbeid, lett industriarbeid, undervisning)
 - Arbeid der du går og løfter mye
(f.eks. postbud, pleier, bygningsarbeider)
 - Tungt kroppsarbeid
- 24 **Angi bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer meget f eks mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.** (Sett kryss i den ruta som passer best)
- Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse
 - Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uken *(her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer med mer)*
 - Driver mosjonsidrett, tyngre hagearbeid, snømåking e.l. *(merk at aktiviteten skal vare minst 4 timer i uka)*
 - Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka
- 25 **Hvor ofte driver du mosjon?** (Med mosjon mener vi at du f.eks går en tur, går på ski, svømmer eller driver trening/idrett)
- Aldri
 - Sjeldnere enn en gang i uken
 - En gang i uken
 - 2-3 ganger i uken +
 - omtrent hver dag

- 26 **Hvor hardt mosjonerer du da i gjennomsnitt?**
- Tar det rolig uten å bli andpusten eller svett.
 - Tar det så hardt at jeg blir andpusten og svett
 - Tar meg nesten helt ut +
- 27 **Hvor lenge holder du på hver gang i gjennomsnitt ?**
- Mindre enn 15 minutter 30 minutter – 1 time
 - 15-29 minutter Mer enn 1 time

ALKOHOL OG TOBAKK

- 28 **Hvor ofte drikker du alkohol?**
- Aldri
 - Månedlig eller sjeldnere
 - 2-4 ganger hver måned
 - 2-3 ganger pr. uke
 - 4 eller flere ganger pr.uke
- 29 **Hvor mange enheter alkohol** (en øl, et glass vin, eller en drink) **tar du vanligvis når du drikker?**
- | | | |
|------------------------------|------------------------------|---|
| <input type="checkbox"/> 1-2 | <input type="checkbox"/> 5-6 | <input type="checkbox"/> 10 eller flere |
| <input type="checkbox"/> 3-4 | <input type="checkbox"/> 7-9 | |
- 30 **Hvor ofte drikker du 6 eller flere enheter alkohol ved en anledning?**
- aldri
 - sjeldnere enn månedlig
 - månedlig
 - ukentlig
 - daglig eller nesten daglig
- 31 **Røyker du av og til, men ikke daglig?**
- Ja Nei
- 32 **Har du røykt/røyker du daglig?**
- Ja, nå Ja, tidligere Aldri
- 33 **Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?**
- Antall år
- 34 **Hvis du røyker daglig nå eller har røykt tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis daglig?**
- Antall sigaretter
- 35 **Hvor gammel var du da du begynte å røyke daglig?**
- Antall år
- 36 **Hvor mange år til sammen har du røykt daglig?**
- Antall år
- 37 **Bruker du, eller har du brukt, snus eller skrå?**
- Nei, aldri Ja, av og til +
 - Ja, men jeg har sluttet Ja, daglig

KOSTHOLD

38 Spiser du vanligvis frokost hver dag?

Ja Nei

39 Hvor mange enheter frukt og grønnsaker spiser du i gjennomsnitt per dag? (Med enhet menes f.eks. en frukt, glass juice, potet, porsjon grønnsaker)

Antall enheter +

40 Hvor mange ganger i uken spiser du varm middag?

Antall

41 Hvor ofte spiser du vanligvis disse matvarene? (Sett ett kryss pr linje)

	0-1 g pr. mnd	2-3 g pr.mnd	1-3 g pr.uke	4-6 g pr.uke	1-2 g pr. dag
Poteter.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pasta/ris.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kjøtt (ikke kvernet).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kvernet kjøtt (pølser, hamburger o.l).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Grønnsaker, frukt, bær..	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mager fisk.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feit fisk..... (f.eks.laks, ørret, makrell, sild, kveite,uer)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

42 Hvor mye drikker du vanligvis av følgende? (Sett ett kryss pr. linje)

	Sjelden/ aldri	1-6 glass pr. uke	1 glass pr. dag	2-3 glass pr. dag	4 glass el. mer pr. dag
Melk, kefir, yoghurt.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fruktjuice.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Brus/leskedrikker med sukker.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

43 Hvor mange kopper kaffe og te drikker du daglig? (sett 0 for de typene du ikke drikker daglig)

	Antall kopper
Filterkaffe.....	<input type="text"/> <input type="text"/>
Kokekaffe/presskanne.....	<input type="text"/> <input type="text"/>
Annen kaffe.....	<input type="text"/> <input type="text"/>
Te.....	<input type="text"/> <input type="text"/>

44 Hvor ofte spiser du vanligvis fiskelever? (For eksempel i mølje)

Sjelden/aldri 1-3 g i året 4-6 g i året
 7-12 g i året Oftere

45 Bruker du følgende kosttilskudd?

	Daglig	Iblant	Nei
Tran, trankapsler.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Omega 3 kapsler (fiskeolje, selolje).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kalktabletter.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SPØRSMÅL TIL KVINNER

46 Er du gravid nå?

Ja Nei Usikker

47 Hvor mange barn har du født?

Antall +

48 Hvis du har født, fyll ut for hvert barn: fødselsår og vekt samt hvor mange måneder du ammet. (Angi så godt som du kan)

Barn	Fødselsår	Fødselsvekt i gram	Ammet ant.mnd
1	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
2	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
4	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
5	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
6	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

49 Har du i forbindelse med svangerskap hatt for høyt blodtrykk?

Ja Nei

50 Hvis Ja, i hvilket svangerskap?

Første Senere

51 Har du i forbindelse med svangerskap hatt protein (eggehvite) i urinen?

Ja Nei

52 Hvis Ja, i hvilket svangerskap?

Første Senere

53 Ble noen av disse barna født mer enn en måned for tidlig (før termin) pga. svangerskapsforgiftning?

Ja Nei

54 Hvis Ja, hvilke(t) barn

Barn 1 Barn 2 Barn 3 Barn 4 Barn 5 Barn 6

55 Hvor gammel var du da du fikk menstruasjon første gang?

Antall år +

56 Bruker du for tiden reseptpliktige legemidler som påvirker menstruasjonen?

P-pille, hormonspiral eller lignende..... Ja Nei
 Hormonpreparat for overgangs-
 alderen..... Ja Nei

VED FRAMMØTE vil du få utfyllende spørsmål om menstruasjon og eventuell bruk av hormoner. Skriv gjerne ned på et papir navn på hormonpreparater du har brukt, og ta det med deg. Du vil også bli spurt om din menstruasjon har opphørt og eventuelt når og hvorfor.

Tromsø

- en del av Tromsøundersøkelsen



1. BESKRIVELSE AV DIN HELSETILSTAND

Vis hvilke utsagn som passer best på din helsetilstand ved å sette ett kryss i en av rutene utenfor hver av de fem gruppene nedenfor:

1.6 For at du skal kunne vise oss hvor god eller dårlig din helsetilstand er, har vi laget en skala (nesten som et termometer), hvor den beste helsetilstanden du kan tenke deg er markert med 100 og den dårligste med 0. Vi ber om at du viser din helsetilstand ved å trekke ei linje fra boksen nedenfor til det punkt på skalaen som passer best med din helsetilstand.

1.1 Gange

- Jeg har ingen problemer med å gå omkring
- Jeg har litt problemer med å gå omkring
- Jeg er sengeliggende

1.2 Personlig stell

- Jeg har ingen problemer med personlig stell
- Jeg har litt problemer med å vaske meg eller kle meg
- Jeg er ute av stand til å vaske meg eller kle meg

1.3 Vanlige gjøremål (f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)

- Jeg har ingen problemer med å utføre mine vanlige gjøremål
- Jeg har litt problemer med å utføre mine vanlige gjøremål
- Jeg er ute av stand til å utføre mine vanlige gjøremål

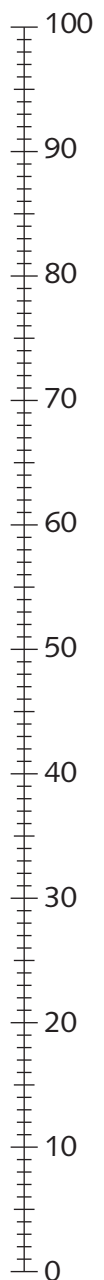
1.4 Smerte og ubehag

- Jeg har verken smerte eller ubehag
- Jeg har moderat smerte eller ubehag
- Jeg har sterk smerte eller ubehag

1.5 Angst og depresjon

- Jeg er verken engstelig eller depriment
- Jeg er noe engstelig eller depriment
- Jeg er svært engstelig eller depriment

Best tenkelige
helsetilstand



Verst tenkelige
helsetilstand

2. OPPVEKST OG TILHØRIGHET

2.1 Hvor bodde du da du fylte 1 år?

- I Tromsø (med dagens kommunegrenser)
- I Troms, men ikke i Tromsø
- I Finnmark fylke
- I Nordland fylke
- Annet sted i Norge
- I utlandet

2.2 Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode
- Gode
- Vanskelige
- Meget vanskelige

2.3 Hvor mange søsken og barn har/har du hatt?

Antall søsken.....

Antall barn.....

2.4 Lever din mor?

- Ja
- Nei

Hvis NEI: alder ved død.....

Lever din far?

- Ja
- Nei

Hvis NEI: alder ved død.....

2.5 Hva var/er den høyeste fullførte utdanning til dine foreldre og din ektefelle/samboer? (sett ett kryss i hver kolonne)

	Mor	Far	Ektefelle/ samboer
Grunnskole 7-10 år, framhaldsskole eller folkehøgskole.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Yrkesfaglig videregående, yrkesskole eller realskole	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Allmennfaglig videregående skole eller gymnas.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Høgskole eller universitet (mindre enn 4 år).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Høgskole eller universitet (4 år eller mer).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2.6 Hva regner du deg selv som? (Kryss av for ett eller flere alternativ)

- Norsk
- Samisk
- Kvensk/Finsk
- Annet

2.7 Hvilken betydning har religion i ditt liv?

- Stor betydning
- En viss betydning
- Ingen betydning

3. TRIVSEL OG LIVSFORHLD

- 3.1 Nedenfor står tre utsagn om tilfredshet med livet som et hele. Vis hvor enig eller uenig du er i hver av de tre påstandene ved å sette ett kryss under det tallet som du synes stemmer best for deg (sett ett kryss for hvert utsagn)

	Helt uenig						Helt enig
	1	2	3	4	5	6	7
På de fleste måter er livet mitt nær idealet mitt.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mine livsforhold er utmerkede.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg er tilfreds med livet mitt.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 3.2 Nedenfor står to utsagn om syn på egen helse. Vis hvor enig eller uenig du er i hver av påstandene ved å sette kryss under det tallet som du synes stemmer best for deg (sett ett kryss for hvert utsagn)

	Helt uenig						Helt enig
	1	2	3	4	5	6	7
Jeg ser lyst på min framtidige helse.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ved å leve sunt kan jeg forhindre alvorlige sykdommer.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 3.3 Nedenfor ber vi deg svare på noen spørsmål om forhold ved din arbeidssituasjon. Dersom du ikke er i arbeid nå, tenk tilbake på den jobben du hadde sist (sett ett kryss for hvert utsagn)

	Ja, ofte	Ja, i blant	Nei, sjelden	Nei, så godt som aldri
Synes du at arbeidet ditt er for belastende, fysisk eller følelsesmessig?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Blir du mobbet eller trakassert på arbeidsplassen din?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Har du tilstrekkelig innflytelse på når og hvordan du skal utføre arbeidet ditt?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Blir du rettferdig behandlet på arbeidsplassen din?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 3.4 Jeg opplever at yrket mitt har følgende status i samfunnet: (dersom du ikke er i arbeid nå, tenk på hvilken status du opplevde av yrket du hadde sist)

Meget høy sosial status

Ganske høy sosial status

Middels status

Ganske lav status

Meget lav status

- 3.5 Har du over lengre tid opplevd noe av det følgende? (sett ett eller flere kryss for hver linje)

	Nei	Ja, som barn	Ja, som voksen	Ja, siste år
Blitt plaget psykisk, eller truet med vold	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Blitt slått, sparket eller utsatt for annen type vold.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Noen i nær familie har brukt rusmidler på en slik måte at dette har vært til bekymring for deg.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Dersom du har opplevd noen av disse forholdene, hvor mye plages du av dette nå?

Ingen plager Noen plager Store plager

4. SYKDOMMER OG PLAGER

4.01 Har du i løpet av den siste måneden følt deg syk eller hatt en skade?

Ja Nei

Hvis JA: har du i den samme perioden? (sett ett eller flere kryss)

- Vært hos allmennlege/fastlege
 Vært hos spesialist
 Vært på legevakt
 Vært innlagt i sykehus
 Vært hos alternativ behandler
(kiropraktor, homøopat eller lignende)
 Tok ikke kontakt med hjelpeapparatet

4.02 Har du merket anfall med plutselig endring i pulsen eller hjerterytmen siste året?

Ja Nei

4.03 Blir du tungpustet i følgende situasjoner? (sett ett kryss for hvert spørsmål)

- | | Ja | Nei |
|--|--------------------------|--------------------------|
| Når du går hurtig på flatmark eller svak oppoverbakke..... | <input type="checkbox"/> | <input type="checkbox"/> |
| Når du spaserer i rolig tempo på flatmark..... | <input type="checkbox"/> | <input type="checkbox"/> |
| Når du vasker deg eller kler på deg..... | <input type="checkbox"/> | <input type="checkbox"/> |
| Når du er i hvile..... | <input type="checkbox"/> | <input type="checkbox"/> |

4.04 Hoster du omtrent daglig i perioder av året?

Ja Nei

Hvis JA: Er hosten vanligvis ledsaget av oppspytt?

Ja Nei

Har du hatt slik hoste så lenge som i en 3 måneders periode i begge de to siste årene?

Ja Nei

4.07 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? (sett ett kryss i hver linje)

	Ikke plaget	En del plaget	Sterkt plaget
Nakke, skuldre.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Armer, hender.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Øvre del av ryggen.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Korsryggen.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hofter, ben, føtter.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Andre steder.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4.05 Hvor ofte er du plaget av søvnløshet? (sett ett kryss)

- Aldri
 1-3 ganger i måneden
 Omtrent 1 gang i uka
 Mer enn 1 gang i uka

Hvis du er plaget av søvnløshet månedlig eller oftere, når på året er du mest plaget? (sett ett eller flere kryss)

- Ingen spesiell tid
 Mørketida
 Midnattsoltida
 Vår og høst

4.06 Nedenfor ber vi deg besvare noen spørsmål om din hukommelse: (sett ett kryss for hvert spørsmål)

	Ja	Nei
Synes du at din hukommelse har blitt dårligere?.....	<input type="checkbox"/>	<input type="checkbox"/>
Glemmer du ofte hvor du har lagt tingene dine?.....	<input type="checkbox"/>	<input type="checkbox"/>
Har du problemer med å finne vanlige ord i en samtale?.....	<input type="checkbox"/>	<input type="checkbox"/>
Har du fått problemer med daglige gjøremål som du mestret tidligere?.....	<input type="checkbox"/>	<input type="checkbox"/>
Har du vært undersøkt for sviktende hukommelse?.....	<input type="checkbox"/>	<input type="checkbox"/>

Hvis JA på minst ett av de fire spørsmålene ovenfor: Er det et problem i hverdagen?

Ja Nei

4.08 **Har du vært plaget med smerter og/eller stivhet i muskler og ledd i løpet av de siste 2 ukene?**
(sett ett kryss i hver linje)

	Ikke plaget	En del plaget	Sterkt plaget
Nakke, skuldre.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Armer, hender.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Øvre del av ryggen.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Korsryggen.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hofte, ben, føtter.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Andre steder.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4.09 **Har du noen gang hatt:**

	Alder		
	Ja	Nei	siste gang
Brudd i håndledd/underarm?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Lårhalsbrudd?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

4.10 **Har eller har du hatt noen av følgende:**

	Aldri	Litt	Mye
Nikkelallergi.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pollenallergi.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Andre allergier.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4.12 **I hvilken grad har du hatt følgende plager i de siste 12 måneder?**

	Aldri	Litt	Mye
Kvalme.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Halsbrann/sure oppstøt.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diare.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Treg mage.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vekslende treg mage og diare.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oppblåsthet.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Smerter i magen.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4.11 **Har du opplevd ufrivillig barnløshet i mer enn 1 år?**

Ja Nei

Hvis JA, skyldtes dette:

	Ja	Nei	Vet ikke
Forhold hos deg selv?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Forhold hos partneren?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4.17 **Bruker du glutenfri diett?**

Ja Nei

4.13 **Til kvinnen: Har du spontanabortert?**

Ja Nei Vet ikke

Hvis JA, antall ganger.....

4.18 **Har du fått stilt diagnosen cøliaki i en vevs-prøve fra tynntarmen under en undersøkelse der du svelget en slange (gastroskopi)?**

Ja Nei

4.14 **Til mannen: Har din partner noen gang spontanabortert?**

Ja Nei Vet ikke

Hvis JA, antall ganger.....

4.19 **Har du fått stilt diagnosen dematitis herpetiformis (HD)?**

Ja Nei

5. KOSTHOLD

5.1 Hvor ofte spiser du vanligvis følgende? (antall ganger) (sett ett kryss i hver linje)

	0-1 g per mnd	2-3 g per mnd	1-3 g per uke	Mer enn 3 g per uke
Ferskvannsfisk (<i>ikke oppdrett</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Saltvannsfisk (<i>ikke oppdrett</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oppdrettsfisk (<i>laks, røye, ørret</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tunfisk (<i>fersk eller hermetisert</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fiskepålegg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Skjell	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Krabbe (<i>den brune innmaten</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hvalkjøtt/sel/kobbekjøtt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Innmat fra rein eller elg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Innmat fra rype	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5.2 Hvor ofte spiser/spiste du vanligvis følgende? (antall ganger)

	Som voksen	I din barndom
Mølje (<i>Antall ganger i året</i>)	<input type="text"/>	<input type="text"/>
Måseegg (<i>Antall egg i året</i>)	<input type="text"/>	<input type="text"/>
Reinsdyrskjøtt (<i>Antall ganger i året</i>)	<input type="text"/>	<input type="text"/>

5.3 Hvor mange ganger i måneden spiser du hermetiske matvarer (fra metallbokser)?

Antall

5.5 Hvor mange ganger i året spiser du vanligvis:

Selvplukket sopp

Selvplukkede bær (*blåbær/tyttebær/multe*)

5.4 Bruker du vitaminer og/eller mineraltilskudd?

Ja, daglig Iblandt Aldri

6. LEVESETT

6.01 **Driver du med følgende fritids- eller yrkesaktiviteter:** Bilreparasjoner/lakkering, keramikk-arbeid, maling/lakkering/løsemidler, frisør, glassmester, elektriker

Antall timer per uke i gjennomsnitt.....

6.02 **Om din tannstatus: Har du egne tenner?**

Ja Nei

6.03 **Hvor mange amalgamfyllinger har du/har du hatt?**

0 1-5 6-10 10+

6.04 **Bruker du hårfargemidler?**

Ja Nei

Hvis JA, hvor mange ganger per år?..

6.05 **Har du ufrivillig gått ned i vekt siste 6 måneder?**

Ja Nei

Hvis JA: Hvor mange kilo?.....

6.06 **Anslå din vekt da du var 25 år gammel:**

Antall kg.....

6.07 **Er du fornøyd med vekta di nå?**

Ja Nei

6.08 **Hvilken vekt ville du være tilfreds med (din trivselsvekt):**

Antall kg.....

6.09 **Hvor ofte har du det siste året:**

	Aldri	Sjeldnere enn månedlig	Månedlig	Ukentlig	Nesten daglig	Daglig
Ikke klart å stoppe og drikke alkohol når du først har begynt?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ikke klart å gjøre det som normalt forventes av deg fordi du har drukket?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Trengt en drink om morgenen for å få komme i gang etter en rangel?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Følt skyld eller anger etter at du har drukket?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ikke klart å huske hva som skjedde kvelden før på grunn av at du hadde drukket?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6.9 **Har du eller andre noen gang blitt skadet på grunn av at du har drukket?.....**

Aldri Ja, men ikke det siste året Ja, det siste året

Har en slektning, venn, lege, eller annet helsepersonell vært bekymret for din drikking, eller foreslått at du reduserer inntaket?...

16. HODEPINE

16.1 Har du vært plaget av hodepine det siste året?

- Ja Nei

Hvis NEI, gå til del 8, bruk av helsetjenester

16.2 Hva slags hodepine er du plaget av?

- Migrene Annen hodepine

16.3 Omtrent hvor mange dager per måned har du hodepine?

- Mindre enn 1 dag
 1-6 dager
 7-14 dager
 Mer enn 14 dager

16.4 Hvor sterk er hodepinen vanligvis?

- Mild (*hemmer ikke aktivitet*)
 Moderat (*hemmer aktivitet*)
 Sterk (*forhindrer aktivitet*)

16.7 Er hodepinen vanligvis:

(sett et kryss pr linje)

- | | Ja | Nei |
|--|--------------------------|--------------------------|
| Bankende/dunkende smerte..... | <input type="checkbox"/> | <input type="checkbox"/> |
| Pressende smerte..... | <input type="checkbox"/> | <input type="checkbox"/> |
| Ensidig smerte (<i>høyre eller venstre</i>)..... | <input type="checkbox"/> | <input type="checkbox"/> |

16.5 Hvor lenge varer hodepinen vanligvis?

- Mindre enn 4 timer
 4 timer – 1 døgn
 1-3 døgn
 Mer enn 3 døgn

16.6 Dersom du er plaget av hodepine, når på året er du plaget mest? (sett ett eller flere kryss)

- Ingen spesiell tid
 Mørketida
 Midnattsoltida
 Vår og/eller høst

16.8 Før eller under hodepinen, kan du ha forbigående:

Ja Nei

- Synsforstyrrelse? (*takkede linjer, flimring, tåkesun, lysglimt*).....
- Nummenhet i halve ansiktet eller i handa?.....
- Forverring ved moderat fysisk aktivitet
- Kvalme og /eller oppkast.....

16.9 Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine:

Antall dager.....

7. BRUK AV HELSETJENESTER

7.01 Har du noen gang opplevd at sykdom er blitt mangelfullt undersøkt eller behandlet, og at dette har gitt alvorlige følger?

- Ja, det har rammet meg selv Ja, det har rammet en nær pårørende Nei
(barn, foreldre, ektefelle/samboer)

Hvis JA, hvor mener du årsaken ligger? (sett ett eller flere kryss):

- | | |
|---|---|
| <input type="checkbox"/> hos fastlege/allmennlege | <input type="checkbox"/> hos annet helsepersonell |
| <input type="checkbox"/> hos legevakslege | <input type="checkbox"/> hos alternativ behandler |
| <input type="checkbox"/> hos privatpraktiserende spesialist | <input type="checkbox"/> hos flere på grunn av svikt i rutiner og samarbeid |
| <input type="checkbox"/> hos sykehuslege | |

7.02 Har du noen gang følt deg overtalt til å godta undersøkelse eller behandling som du selv ikke ønsket?

- Ja Nei

Hvis JA, mener du dette har hatt uheldige helsemessige følger?

- Ja Nei

7.03 Har du noen gang klaget på behandling du har fått?

- Har aldri vært aktuelt
 Har vurdert å klage, men ikke gjort det
 Har klaget muntlig
 Har klaget skriftlig

7.04 Hvor lenge har du hatt din nåværende fastlege/annen lege?

- Mindre enn 6 mnd
 6 til 12 mnd
 12 til 24 mnd
 Mer enn 2 år

7.05 Har du en kronisk sykdom eller tilstand som påvirker din arbeidsevne eller dine daglige aktiviteter?

- Ja Nei

7.06 Opplever du at fastlegen din har god nok forståelse for hvordan denne sykdommen eller tilstanden påvirker dine daglige aktiviteter?

- Ja Nei Vet ikke

7.07 Snakket legen(e) til deg slik at du forsto dem?

Svar på en skala fra 0 til 10, hvor 0=de var vanskelige å forstå og 10=de var alltid enkle å forstå

- 0 1 2 3 4 5 6 7 8 9 10

7.08 Hvordan vil du karakterisere behandlingen eller rådgivningen du fikk siste gang du var hos lege? Svar på en skala fra 0 til 10, hvor 0= meget dårlig behandling og 10 = meget god behandling

- 0 1 2 3 4 5 6 7 8 9 10

7.09 Har du i løpet av de siste 12 mnd opplevd at det har vært vanskelig å bli henvist til spesielle undersøkelser (som røntgen eller liknende) eller til spesialisthelsetjenesten? (privatpraktiserende spesialist eller ved sykehus)

- Ikke aktuelt
 Intet problem
 Noe problem
 Stort problem

7.10 Har du i løpet av de siste 12 mnd opplevd at det er vanskelig å bli henvist til fysioterapeut, kiropraktor eller liknende?

- Ikke aktuelt
 Intet problem
 Noe problem
 Stort problem

7.11 **Alt i alt, har du opplevd at det er vanskelig eller enkelt å bli henvist til spesialisthelsetjenesten?**

- Ikke aktuelt
- Meget vanskelig
- Noe vanskelig
- Rimelig enkelt
- Meget enkelt

7.12 **Har du i løpet av de siste 12 måneder vært til undersøkelse eller behandling i spesialisthelsetjenesten?**

- Ja
- Nei

Hvis JA, snakket legen(e) til deg slik at du forstod dem? Svar på en skala fra 0 til 10, hvor 0=de var vanskelige å forstå og 10=de var alltid enkle å forstå

- 0 1 2 3 4 5 6 7 8 9 10
-

7.13 **Hvordan vil du karakterisere erfaringen med spesialisten du sist møtte?** Svar på en skala fra 0 til 10, hvor 0 =meget dårlig erfaring og 10=meget god erfaring

- 0 1 2 3 4 5 6 7 8 9 10
-

7.16 **Har du noen gang før 2001 gjennomgått en operasjon på sykehus eller spesialistklinik?**

- Ja
- Nei

7.14 **Har du i løpet av de siste 12 måneder brukt urtemedisin, naturmidler eller naturlegemidler?**

- Ja
- Nei

7.15 **Har du i løpet av de siste 12 måneder brukt meditasjon, yoga, qi gong eller thai chi som egenbehandling?**

- Ja
- Nei

8. BRUK AV ANTIBIOTIKA

8.1 Har du brukt antibiotika i løpet av de siste 12 måneder? (all penicillinliknende medisin i form av tabletter, mikstur eller sprøyter)

Ja Nei Husker ikke

	Kur 1	Kur 2	Kur 3	Kur 4	Kur 5	Kur 6
Hva fikk du behandling mot?						
· Urinveisinfeksjon (blærebetennelse, blærekatarr).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
· Luftveisinfeksjon (øre-, bihule- hals- eller lungebetennelse)...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
· Annet.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Antall dagers antibiotika kur.....	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Etter resept fra lege/tannlege.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Uten kontakt med lege/uten resept:						
· Kjøp direkte fra apotek i utlandet.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
· Kjøp gjennom Internett.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
· Rest fra tidligere kur til gjengelig hjemme.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
· Fått av familie/venner.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
· Andre måter.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8.2 Har du antibiotika hjemme nå?

Ja Nei

Hvis JA, er dette etter avtale med lege/tannlege?

Ja Nei

Hvis NEI, hvordan skaffet du deg dette legemiddelet?

Kjøp direkte fra apotek i utlandet.....

Kjøp gjennom Internett.....

Fått av familie/venner.....

Andre måter.....

8.3 Dersom du har antibiotika hjemme, vil du starte behandling uten å kontakte lege?

Ja Nei

Hvis JA, hvilke tilstander vil du i så fall behandle?

Forkjølelse.....

Hoste.....

Bronkitt.....

Halsbetennelse.....

Bihulebetennelse.....

Feber.....

Influensa.....

Ørebetennelse.....

Diaré.....

Blærebetennelse.....

Andre infeksjoner (beskriv under).....

9. DIN DØGNRYTME

Vi vil spørre deg noen spørsmål som handler om dine søvnvaner når du ikke kan velge fritt når du må stå opp.

9.1 Antall dager i løpet av uken hvor du ikke kan velge fritt når du vil sove (f.eks arbeidsdager)?

0 1 2 3 4 5 6 7

Når jeg ikke kan velge fritt når jeg skal sove, da:

Går jeg til sengs klokken.....

Jeg gjør meg klar til å sove klokken.....

Antall minutter jeg trenger på å sovne.....

Jeg våkner klokken.....

Ved hjelp av: Vekkeklokke annen ytre påvirkning (*støy, familie etc*) av meg selv

Antall minutter jeg trenger på å stå opp.....

Vi vil spørre deg noen spørsmål som handler om dine søvnvaner når du kan velge fritt når du må stå opp.

9.2 De neste spørsmålene vil vi spørre deg om dine søvnvaner når du fritt kan velge når du vil stå opp:

0 1 2 3 4 5 6 7

Når jeg kan velge fritt når jeg skal sove, da:

Går jeg til sengs klokken.....

Jeg gjør meg klar til å sove klokken.....

Antall minutter jeg trenger på å sovne.....

Jeg våkner klokken.....

Ved hjelp av: Vekkeklokke annen ytre påvirkning (*støy, familie etc*) av meg selv

Antall minutter jeg trenger på å stå opp.....

9.3 Har du hatt skiftarbeid de tre siste månedene?

Ja Nei

10. HUD OG HUDSYKDOMMER

10.1 **Hvor ofte dusjer eller bader du vanligvis?**
(sett ett kryss)

- 2 eller flere ganger daglig
 1 gang daglig
 4-6 ganger per uke
 2-3 ganger per uke
 1 gang per uke
 sjeldnere enn en gang per uke

10.3 **Hvor ofte vasker du vanligvis hendene dine med såpe i løpet av en dag?**

- 0-5 ganger
 6-10 ganger
 11-20 ganger
 Mer enn 20 ganger

10.2 **Vasker du kroppen (inkludert armer og ben) med såpe når du dusjer eller bader?**

- Ja Nei

10.4 **Har du noen gang fått antibiotikakur (penicillin og liknende medisin) på grunn av en hudlidelse, for eksempel betent eksem, kviser, leggsår som ikke vil gro, tilbakevendende verkebyll?**

- Ja Nei

Hvis JA: Hvor mange ganger i året fikk du antibiotika i den perioden du var rammet?

- 1-2 3-4 Mer enn 4 ganger

10.5 **Har du ofte eller bestandig noen av følgende plager?** (sett ett kryss for hver linje)

- Hevelse i ankler og legger, særlig om kvelden..... Ja Nei
Eksem (rødt, kløende utslett) på leggene..... Ja Nei
Smarter i beina når du går, men som forsvinner når du står stille..... Ja Nei

10.6 **Har du eller har du noen gang hatt følgende plager?** (sett ett kryss for hver linje)

- Psoriasis?..... Ja Nei
Atopisk eksem (barneeksem)?..... Ja Nei
Tilbakevendende håndeksem?..... Ja Nei
Tilbakevendende kviser over flere måneder?..... Ja Nei
Legg- eller fotsår som ikke ville gro i løpet av 3-4 uker?..... Ja Nei

Hvis JA på spørsmål om legg-og/eller fotsår, har du leggsår i dag?

- Ja Nei

10.8 **Har du noen gang fått følgende diagnoser av lege?**

- Psoriasis..... Ja Nei
Atopisk eksem..... Ja Nei

10.7 **Har du plager i form av tilbakevendende kviser/verkebyll, som er ømme/smertefulle og som ofte tilheler med arr, på noen av de følgende stedene på kroppen?**

- Armhulene..... Ja Nei
Under brystene..... Ja Nei
Magefolden..... Ja Nei
Rundt kjønnsorgan..... Ja Nei
Rundt endetarmsåpning..... Ja Nei
Lysker..... Ja Nei

10.8 **Har du noen gang oppsøkt lege på grunn av dine plager med verkebyll?**

- Ja Nei

Hvis JA, fikk du da noen av følgende behandlinger?

- Antibiotika salve/krem..... Ja Nei
Antibiotika tablett..... Ja Nei
Større kirurgisk inngrep med fjerning av hud..... Ja Nei
Kirurgisk laserbehandling..... Ja Nei

Informasjon til oppfølgingsspørsmålene



11. OPPFØLGINGSPØRSMÅL KRONISK SMERTE

Du svarte i det første spørreskjemaet at du har eller har hatt langvarige eller stadig tilbakevendende smerter i mer enn 3 måneder. Her er noen oppfølgingsspørsmål vi håper du vil svare på

11.1 På en skala fra 0 til 10, der 0 tilsvarer ingen smerte og 10 tilsvarer den sterkeste smerten du kan forestille deg:

	Ingen smerte										Verst tenkelige smerte
	0	1	2	3	4	5	6	7	8	9	10
Hvor sterke vil du si at smertene vanligvis er?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hvor sterke er smertene når de er på sitt sterkeste?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Påvirker ikke										Umulig å få sove
	0	1	2	3	4	5	6	7	8	9	10
I hvor stor grad påvirker smertene søvnen din?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Påvirker ikke										Kan ikke gjøre noe
	0	1	2	3	4	5	6	7	8	9	10
I hvor stor grad hindrer smertene deg i å utføre vanlige aktiviteter hjemme og i arbeid?.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11.2 Hvor lenge har du hatt disse smertene?

Antall år..... måneder.....

11.3 Hvor ofte har du vanligvis disse smertene?

- | | |
|---|--|
| <input type="checkbox"/> Hver dag | <input type="checkbox"/> En eller flere ganger i måneden |
| <input type="checkbox"/> En eller flere ganger i uken | <input type="checkbox"/> Sjeldnere enn 1 gang i måneden |

11.4 Hvor er det vondt? (Kryss av for alle steder der du har langvarige eller stadig tilbakevendende smerter)

- | | |
|--------------------------------------|---|
| <input type="checkbox"/> Hode/ansikt | <input type="checkbox"/> Lår/kne/legg |
| <input type="checkbox"/> Nakke | <input type="checkbox"/> Ankel/fot |
| <input type="checkbox"/> Rygg | <input type="checkbox"/> Bryst |
| <input type="checkbox"/> Skulder | <input type="checkbox"/> Mage |
| <input type="checkbox"/> Arm/albue | <input type="checkbox"/> Underliv/kjønnsorganer |
| <input type="checkbox"/> Hånd | <input type="checkbox"/> Hud |
| <input type="checkbox"/> Hofte | <input type="checkbox"/> Annet sted |

11.5 Hvilke former for behandling har du fått for smertene? (Kryss av for alle typer smertebehandling du har mottatt)

- | | |
|---|---|
| <input type="checkbox"/> Ingen behandling | <input type="checkbox"/> Smerteskole/avspenning/psykoterapi |
| <input type="checkbox"/> Smertestillende medisiner | <input type="checkbox"/> Akupunktur |
| <input type="checkbox"/> Fysioterapi/kiropraktikk | <input type="checkbox"/> Alternativ behandling (<i>homøopati, healing, aromaterapi, m.m.</i>) |
| <input type="checkbox"/> Behandling ved smerteklinikk | <input type="checkbox"/> Annen behandling |
| <input type="checkbox"/> Operasjon | |

11.6 Hva mener du er årsaken til smertene? (Kryss av for alle kjente årsaker)

- | | |
|---|--|
| <input type="checkbox"/> Ulykke/akutt skade | <input type="checkbox"/> Fibromyalgi |
| <input type="checkbox"/> Langvarig belastning | <input type="checkbox"/> Angina pectoris (<i>hjertekrampe</i>) |
| <input type="checkbox"/> Kirurgisk inngrep/operasjon | <input type="checkbox"/> Dårlig blodsirkulasjon |
| <input type="checkbox"/> Skiveutglidning (<i>prolaps</i>)/lumbago | <input type="checkbox"/> Kreft |
| <input type="checkbox"/> Nakkesleng (<i>whiplash</i>) | <input type="checkbox"/> Nerveskade/nevropati |
| <input type="checkbox"/> Migrene/hodepine | <input type="checkbox"/> Infeksjon |
| <input type="checkbox"/> Slitasjegikt (<i>artrose</i>) | <input type="checkbox"/> Helvetesild |
| <input type="checkbox"/> Leddgikt | <input type="checkbox"/> Annen årsak (<i>beskriv under</i>) |
| <input type="checkbox"/> Bekhtrevs sykdom | <input type="checkbox"/> Vet ikke |

Beskriv annen årsak:

.....

12. OPPFØLGINGSSPØRSMÅL OPERASJON

I det første spørreskjemaet svarte du at du har gjennomgått en operasjon i løpet av de siste tre årene. Nedenfor ber vi deg om å svare på noen spørsmål om den siste operasjonen du har gjennomgått.

12.1 **Den siste operasjonen du gjennomgikk, hvor i kroppen ble du operert?** (Dersom du samtidig ble operert flere steder i kroppen, settes flere kryss)

	Siste operasjon
Operasjon i øvre del av kroppen.....	<input type="checkbox"/>
· Hode/ansikt.....	<input type="checkbox"/>
· Nakke/hals.....	<input type="checkbox"/>
· Rygg.....	<input type="checkbox"/>
Operasjoner i brystregionen.....	<input type="checkbox"/>
· Hjerte.....	<input type="checkbox"/>
· Lunger.....	<input type="checkbox"/>
· Bryster.....	<input type="checkbox"/>
Operasjon i magen.....	<input type="checkbox"/>
· Mage/tarm.....	<input type="checkbox"/>
· Lyskebrokk.....	<input type="checkbox"/>
· Urinveier/kjønnsorganer.....	<input type="checkbox"/>
· Andre indre organer i magen.....	<input type="checkbox"/>
Operasjoner i hofte/ben.....	<input type="checkbox"/>
· Hofte/lår.....	<input type="checkbox"/>
· Kne/legg.....	<input type="checkbox"/>
· Ankel/fot.....	<input type="checkbox"/>
· Amputasjon.....	<input type="checkbox"/>
Skulder/Arm.....	<input type="checkbox"/>
· Skulder/overarm.....	<input type="checkbox"/>
· Albue/underarm.....	<input type="checkbox"/>
· Hånd.....	<input type="checkbox"/>
· Amputasjon.....	<input type="checkbox"/>

12.2 **Bakgrunn for operasjonen:**

Akutt sykdom/skade.....	<input type="checkbox"/>
Planlagt ikke kosmetisk operasjon.....	<input type="checkbox"/>
Planlagt kosmetisk operasjon.....	<input type="checkbox"/>

12.3 **Hvor ble du operert?**

Universitetssykehuset i Nord-Norge (UNN).....	<input type="checkbox"/>
Sykehuset i Harstad.....	<input type="checkbox"/>
Annet offentlig sykehus.....	<input type="checkbox"/>
Privat klinikk.....	<input type="checkbox"/>

12.4 **Smerte fra operasjonsstedet:** Svar på en skala fra 0 til 10, hvor 0=ingen smerte og 10=verst tenkeligs smerte

Ingen smerte
0 1 2 3 4 5 6 7 8 9 10
Verst tenkelige smerte

Hvor sterke smerter hadde du fra operasjonsstedet før operasjonen.....

Hvor sterke smerter har du vanligvis fra operasjonsstedet nå.....

Hvor sterke smerter har du fra operasjonsstedet når smertene er på det sterkeste.....

12.5 **Hvor lenge er det siden du gjennomgikk operasjonen?**

Antall år..... måneders.....

12.8 **Kan lett berøring av klær, dusj og lignende fremkalle ubehag/smerte?**

Ja Nei

12.6 **Har du nedsatt følsomhet i et område nær operasjonsarret?**

Ja Nei

12.9 **Hvis du hadde smerter på operasjonsstedet før du ble operert, har du den samme type smerte nå?**

Ja Nei

12.7 **Er du overfølsom for berøring, varme eller kulde i et område nær operasjonsarret?**

Ja Nei

12.10 **Hvor mange operasjoner har du totalt gjennomgått?**

Antall.....

17. OPPFØLGINGSSPØRSMÅL ARBEID I KALDT KLIMA

I det første spørreskjemaet svarte du ja på at du arbeidet i kaldt klima. Her er noen oppfølgings-spørsmål vi håper du vil svare på.

17.1 Fryser du på jobb?

- Ja, ofte
 Ja, noen ganger
 Nei, aldri

17.2 Hvor lenge har du vært utsatt for kalde omgivelser under 0°C sist vinter?

Fritid/hobby (timer/uke).....

Arbeid (timer/uke).....

Utendørs, godt kledd (timer/uke).....

Utendørs, tynnkledd (timer/uke).....

Innendørs, uten oppvarming (timer/uke).....

I kalde omgivelser, med våte klær (timer/uke).....

Kontakt med kalde gjenstander/verktøy (timer/uke).....

17.3 Hvilken omgivelsestemperatur forhindrer deg i å:

Fra °C

Arbeide utendørs.....

Trene utendørs.....

Utføre andre aktiviteter utendørs.....

17.4 Har du hatt forfrysninger siste 12 måneder, med blemmer, sår eller skader i huden?

- Ja Nei

Hvis JA, hvor mange ganger?.....

17.5 Har du opplevd kløe og/eller utslett i forbindelse med kulde?

- Ja Nei

17.6 Har du i løpet av de siste 12 måneder vært involvert i ulykke som krevde medisinsk behandling der kulde var en viktig faktor?

Ja Nei

På arbeid.....

I fritiden.....

17.7 Opplever du noen av følgende symptomer mens du oppholder deg i kalde omgivelser? I så fall, ved hvilken temperatur oppstår symptomene?

	Ja	Nei	Fra °C
Pusteproblemer.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Pipende pust.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Slim fra lungene.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Brystsmerter.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Forstyrrelse i hjerterytmen.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Nedsatt blodsirkulasjon i hender/føtter.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Synsforstyrrelse (kortvarig/forbigående).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Migrene (kortvarig/forbigående).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Hvite fingre (kortvarig/forbigående).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Blå, blå-røde fingre (kortvarig/forbigående).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

17.8 Hvordan påvirker kalde omgivelser og kulderelaterte symptomer din yteevne?

	Ingen	Nedsatt	Forbedret
Konsentrasjon.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hukommelse.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fingerfølsomhet (følelse).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fingerferdighet (motorikk).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kontroll av bevegelse (for eksempel skjelving).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tungt fysisk arbeid.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Langvarig fysisk arbeid.....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

18. BRUK AV RESEPTFRIE SMERTESTILLENDENDE LEGEMIDLER

I det første spørreskjemaet svarte du at du hadde brukt reseptfrie smertestillende legemidler de siste 4 ukene. Her er noen oppfølgingsspørsmål vi håper du vil svare på.

18.1 **Paracetamol:** (*Pamol, Panodil, Paracet, Paracetamol, Pinex*)

- Ikke brukt
- Sjeldnere enn hver uke
- Hver uke, men ikke daglig
- Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?

(Antall tabletter, pulver, stikkpiller).....

18.5 **Fenazon med koffein:** (*Antineuralgica, Fanalgin, Fenazon-koffein, Fenazon-koffein sterke*)

- Ikke brukt
- Sjeldnere enn hver uke
- Hver uke, men ikke daglig
- Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?

(Antall tabletter, pulver, stikkpiller).....

18.2 **Acetylsalisylsyre:** (*Albyl-E, Aspirin, Dispril, Globoid*)

- Ikke brukt
- Sjeldnere enn hver uke
- Hver uke, men ikke daglig
- Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?

(Antall tabletter, pulver, stikkpiller).....

18.6 **Diklofenak:** (*Otriflu*)

- Ikke brukt
- Sjeldnere enn hver uke
- Hver uke, men ikke daglig
- Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?

(Antall tabletter, pulver, stikkpiller).....

18.3 **Ibuprofen:** (*Ibumetin, Ibuprofen, Ibuprox, Ibox*)

- Ikke brukt
- Sjeldnere enn hver uke
- Hver uke, men ikke daglig
- Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?

(Antall tabletter, pulver, stikkpiller).....

18.7 **Mener du å ha opplevd bivirkninger av noen av legemidlene?** (sett ett kryss for hver linje)

	Ja	Nei
Paracetamol.....	<input type="checkbox"/>	<input type="checkbox"/>
Acetylsalisylsyre.....	<input type="checkbox"/>	<input type="checkbox"/>
Ibuprofen.....	<input type="checkbox"/>	<input type="checkbox"/>
Naproxen.....	<input type="checkbox"/>	<input type="checkbox"/>
Fenazon med koffein.....	<input type="checkbox"/>	<input type="checkbox"/>
Diklofenak.....	<input type="checkbox"/>	<input type="checkbox"/>

18.4 **Naproxen:** (*Naprosyn, Naproxen*)

- Ikke brukt
- Sjeldnere enn hver uke
- Hver uke, men ikke daglig
- Daglig

Hvor mye tar du vanligvis daglig når du bruker midlene?

(Antall tabletter, pulver, stikkpiller).....

18.8 **Kombiner du behandlingen med bruk av reseptbelagte smertestillende midler?**

- Ja
- Nei

18.9 **Hvor pleier du å kjøpe slike legemidler?**

- Apotek
- Dagligvare
- Bensinstasjon
- Utenlands
- Internett

19. OPPFØLGINGSSPØRSMÅL HUDSYKDOMMER

På side... i dette spørreskjemaet svarte du at du har eller hatt en hudsykdom. Her er noen oppfølgings spørsmål vi håper du vil svare på.

	Ingen plager	0	1	2	3	4	5	6	7	8	9	10	Verst tenkelige plager
19.1 Dersom du svarte ja på at du har hatt eller har psoriasis:													
· Hvor mye plaget er du av din psoriasis i dag?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
· Hvordan vurderer du graden av din psoriasis når den er som verst?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19.2 Dersom du svarte ja på at du har eller har hatt atopisk eksem:													
· Hvor mye plaget er du av ditt atopiske eksem i dag?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
· Hvordan vurderer du graden av ditt atopiske eksem når det er som verst?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19.3 Dersom du svarte ja på at du har eller har hatt håndeksem:													
· Hvor mye plaget er du av din håndeksem i dag?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
· Hvordan vurderer du graden av ditt håndeksem når det er som verst?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19.4 Dersom du svarte ja på at du noen gang har vært plaget av tilbakekallende kviser:													
· Hvor mye plaget er du av dine med kviser i dag?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
· Hvordan vurderer du graden av dine plager med kviser når det er som verst?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19.5 Dersom du svarte ja på at du har vært eller er plaget med verkebyller:													
· Hvordan vurderer du plagene dine med verkebyller i dag?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
· Hvordan vurderer du graden av dine plager med verkebyller når det er som verst?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19.7 Her er en liste over faktorer som kan tenkes å utløse eller forverre verkebyller, kryss av for hva du synes gjelder for deg:													
		Ja	Nei										
Stress/psykisk påkjenning		<input type="checkbox"/>	<input type="checkbox"/>										
Trange/tette klær		<input type="checkbox"/>	<input type="checkbox"/>										
Menstruasjonsyklus		<input type="checkbox"/>	<input type="checkbox"/>										
Svangerskap		<input type="checkbox"/>	<input type="checkbox"/>										
Annet		<input type="checkbox"/>	<input type="checkbox"/>										
19.6 Hvor gammel var du da du fikk verkebyller første gang?													
		<input type="checkbox"/>	0-12 år			<input type="checkbox"/>	26-35 år						
		<input type="checkbox"/>	13-19 år			<input type="checkbox"/>	36-50 år						
		<input type="checkbox"/>	20-25 år			<input type="checkbox"/>	50+ år						
19.8 Dersom du ikke lengre er plaget hvor gammel var du da plagene forsvant?													
		<input type="checkbox"/>	0-12 år			<input type="checkbox"/>	26-35 år						
		<input type="checkbox"/>	13-19 år			<input type="checkbox"/>	36-50 år						
		<input type="checkbox"/>	20-25 år			<input type="checkbox"/>	50+ år						



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