UiT The Arctic University of Norway

Faculty of Health Sciences, Department of Clinical Medicine

Trends for cognitive function and dementia in a general population; Risk factors, trajectories, and incidence.

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A dissertation for the degree of Philosophiae Doctor. January 2024.

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Acknowledgements

The journey of pursuing a PhD has been an experience filled with gratitude, surprise, and excitement, as well as moments of frustration, impatience, and self-doubt. The research process has been enlightening both on a personal level and as a theoretical eruption of knowledge. I am deeply grateful to have the opportunity to be a part of this captivating field of research and to collaborate with such inspiring people. Certain individuals deserve special recognition for their contribution.

My main supervisor, *Henrik Schirmer*. This intelligent, experienced and inspirational researcher has done an immense job guiding, motivating and assisting me through the process. He has helped me interpret my results, corrected my English, and reviewed my articles countless times. He dedicated both his leisure and work time to support me, for which I am profoundly grateful.

I want to extend my gratitude to my co-supervisor and on-site mentor, *Ieva Martinaityte*, who is not only a dear friend but also an inspiring individual. Your wisdom, boundless energy, and profound passion for the elderly have truly been a source of inspiration. Your constant motivation and hands-on guidance have been invaluable in helping me navigate through intricate details.

My co-authors: Bjørn Heine Strand, Ellisiv B. Mathiesen, Geir Lorem and Tom Wilsgård. Each of you have made significant contributions with your expertise in research, methods, statistics, and analysis, which have all been instrumental in shaping the papers. A special thanks to Heine, who have been so kind to also include me in other research projects.

I would also like to extend my gratitude to all the wonderful individuals at The Tromsø Study for their support, patience, and assistance. I am looking forward to collaborations in the future.

Further, a special thanks to Elena Kamycheva, my first boss and supervisor at the Department of Geriatrics. Thank you for introducing me to this project and advocating for Henrik to supervise me. To my next boss, Gunhild Ag, and all the remarkable individuals at the Department of Geriatrics, your support has been invaluable throughout this journey. By allowing me to work clinically with geriatric patients, you've kept me grounded and reminded me that behind every statistic and figure lies someone's destiny. The same gratitude goes to my newest employer, the

Emergency Medicine Unit, for generously accommodating my research commitments and enabling me to successfully complete my dissertation while in their service. Their support has been instrumental, allowing me to balance work responsibilities with academic pursuits effectively. To the members of the Endocrinology and Geriatrics Research Group: I extend my heartfelt appreciation for your valuable input and inspiration.

Lastly, but of utmost importance, my deepest gratitude goes to my loved ones at home. My darling kids, Julia, Teodor, Matja and Ella who likes that I study “Remembering diseases”. You are my everything, and I am incredibly proud of you all! To my husband, Marius, who has both challenged and supported me, serving as a rock-solid and intellectually stimulating discussion partner, as well as a buffer during moments of frustration. Thankfully you wrote your PhD first, so you understood my process, and remained brave even when I almost bested you in the Forsker Grand Prix. Love you all!

To my parents, sister, brother-in-law, and their children: I am profoundly grateful for the serene moments at Rostadalen that have allowed me to return to a resting heart rate. Your hours of dedicated babysitting have been an incredible support. I eagerly anticipate more campfires by the lake together in the future.

Abbreviations and definitions

ADL	Activity of Daily Living
AIC	Akaike Information Criterion
BDNF	Brain-derived Neurotrophic Factor
BMI	Body Mass Index
CI	Confidence Interval
CR	Cognitive Reserve
CSVD	Cerebral Small Vessel Disease
CVD	Cardiovascular disease
HIC	High Income Countries
IQ	Intelligence Quotient
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
PA	Physical Activity
Preclinical phase of dementia	Usually, findings of dementia pathology without clinical symptoms (1). In this thesis it means participants who have not yet received a MCI or dementia diagnose
SD	Standard Deviation
VO2max	Maximum Volume of O2 in litres/minute

List of papers

Paper 1

Bente Johnsen, Bjørn Heine Strand, Ieva Martinaityte, Ellisiv B. Mathiesen, Henrik Schirmer

"Improved Cognitive Function in the Tromsø Study in Norway From 2001 to 2016."

Neurology Clinical Practice, December 2021, 11 (6) e856-e866;
DOI: 10.1212/CPJ.0000000000001115

Paper 2

Bente Johnsen, Ieva Martinaityte, Tom Wilsgaard, Henrik Schirmer.

"Incidence of dementia over a period of 20 years in a Norwegian population."

Alzheimer's Dement. 2023; 15:e12479. https://doi.org/10.1002/dad2.12479

Paper 3

Bente Johnsen, Bjørn Heine Strand, Ieva Martinaityte, Geir Lorem, Henrik Schirmer.

"Leisure Time Physical Activities' Association With Cognition and Dementia: A 19 Years' Life Course Study."

Frontiers Aging Neuroscience. 2022 Jun 15;14:906678. doi: 10.3389/fnagi.2022.906678. PMID: 35783131; PMCID: PMC9241436. DOI: 10.3389/fnagi.2022.906678

Summary

With increasing life expectancy, healthy cognitive aging is important for a fulfilling life in old age. While cognitive health in young adults has shown improvement over the past century, there remains a scarcity of longitudinal studies on people over the age of 60. Risk and protective factors for dementia and cognitive decline have been identified, and one of the most promising protective factors is physical activity. Notably, dementia prevalence in Norway exceeds that of comparable countries, yet longitudinal incidence studies are lacking. As of 2021, dementia stands as the third leading cause of death in Norway, emphasizing the urgency of comprehensive research in this domain. The aim of this study was to analyse cognitive trajectories in middle-aged and old adults, while investigating the association between risk factors and cognition, as well as dementia. Additionally, the study aimed to examine the incidence of dementia. The data utilized in this research was obtained from the Tromsø Study, an ongoing longitudinal population-based study that has been conducting repeated health surveys since 1974, including cognitive tests since 2001. In the initial phase of our study, we examined cognitive trajectories in participants aged 60 and above. Subsequently, we established an endpoint registry for dementia by identifying all individuals who participated in The Tromsø Study and later received a dementia diagnosis. From this we calculated incidence of dementia over a 20-year period. Furthermore, we studied cognitive function by stratifying participants into physically active and inactive groups, both among those who were cognitive healthy and those later received a dementia diagnosis. We found that individuals performed better on cognitive tests compared to previous generations at the same age. Furthermore, we observed that women mostly outperformed men. Cognition was positively associated with higher levels of education, increased physical activity and increased alcohol consumption frequency, but not increased units of alcohol. For men, there were additional positive associations found with smoking cessation and increased height. We also uncovered a significant decrease in dementia by up to 61% over the last two decades, in those over 60 years of age. The 5-year incidence rate per 1000 people was 1.1 in 60–69-year-olds, 7.7 in 70–79-year-olds, 30.1 in 80–89-year-olds and 52.8 in those above 90 years of age. Physical activity was positively associated with high test scores on cognitive tests, but surprisingly, only in those who remained dementia free. The study's results suggested that cognitive capability continues to increase among middle-aged and older adults, and that age-specific dementia incidence is decreasing.

Sammendrag

Med økende levealder er kognitiv sunn aldring viktig for et godt liv i alderdommen. Kognisjon hos unge voksne har økt det siste århundret, men det er få studier over tid på personer over 60 år. Risikofaktorer og beskyttende faktorer for kognitiv svikt og demens er identifisert, og en av de mest lovende beskyttende faktorer er fysisk aktivitet. Samtidig er demensprevalensen høyere i Norge enn sammenlignbare land, og longitudinelle insidensstudier mangler.

Formålet med doktorgraden var å analysere kognisjon over tid hos middelaldrende og eldre voksne, samt undersøke sammenhengen mellom risikofaktorer, kognisjon og demens. Studien hadde også som mål å undersøke insidens av demens. Data ble hentet fra Tromsøundersøkelsen og sykehusjournaler.

I den innledende fasen av studien undersøkte vi kognitiv utvikling over tid hos deltakere i alderen over 60 år. Deretter lagde vi et endepunktsregister for demens ved å identifisere alle personer som hadde deltatt på Tromsøundersøkelsen og senere fått en demensdiagnose. Ut fra dette beregnet vi insidens av demens over en 20-årsperiode. Videre utforsket vi kognitiv funksjon over tid, hvor deltakerne ble delt inn i fysisk aktive og inaktive grupper, både blant de som var kognitivt friske og de som senere fikk demens.

Vi fant at individer presterte bedre på kognitive tester enn tidligere generasjoner på samme alder, og at kvinner stort sett presterte bedre enn menn. Kognisjon var positivt assosiert med høyere utdanningsnivå, økt fysisk aktivitet, flere anledninger med alkoholinntak, men ikke økt antall alkoholenheter. For menn var det også positiv sammenheng med røykeslutt og økt høyde. Vi avdekket også en betydelig nedgang i demensforekomsten de siste to tiårene hos de over 60 år, med opptil 61 %. 5-års insidensraten per 1000 personer var 1.1 hos 60-69 år, 7.7 hos 70-79 år, 30.1 hos 80-89 år og 52.8 hos de over 90 år.

Fysisk aktivitet var positivt assosiert med høyere testscore på kognitive tester, men overraskende nok bare hos de som forble demensfrie. Studiens resultater antydet at kognitiv kapasitet fortsetter å øke blant middelaldrende og eldre voksne, og at insidens av demens er synkende.

1 Introduction

In a historical first, we are on the brink of a demographic shift in Norway where the population over 65 years of age is poised to outnumber those under 20 years of age (Figure 1) (2). For the North of Norway we reached this breaking point in 2023 (2). This trend is mostly attributed to enhanced life expectancy due to improved medical and preventive treatments, enabling survival from once-fatal diseases or evading them entirely, as well as increased hygiene, education and diet (3).

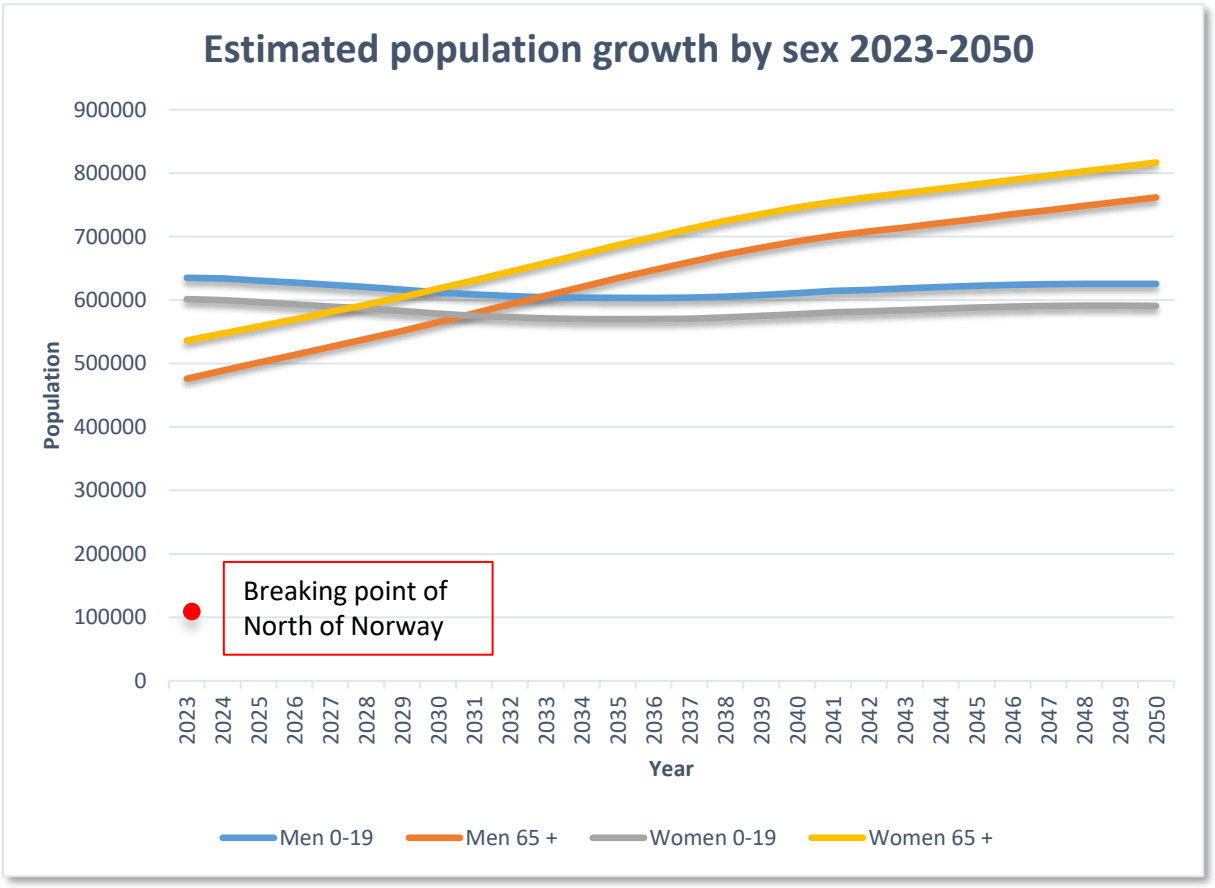


Figure 1: Estimated population growth from year 2023 to 2050, stratified by sex. The numbers are extracted from "Statistics Norway" table 13599 (4). The projected numbers are using the main alternative of mean fertility, life expectancy and immigration.

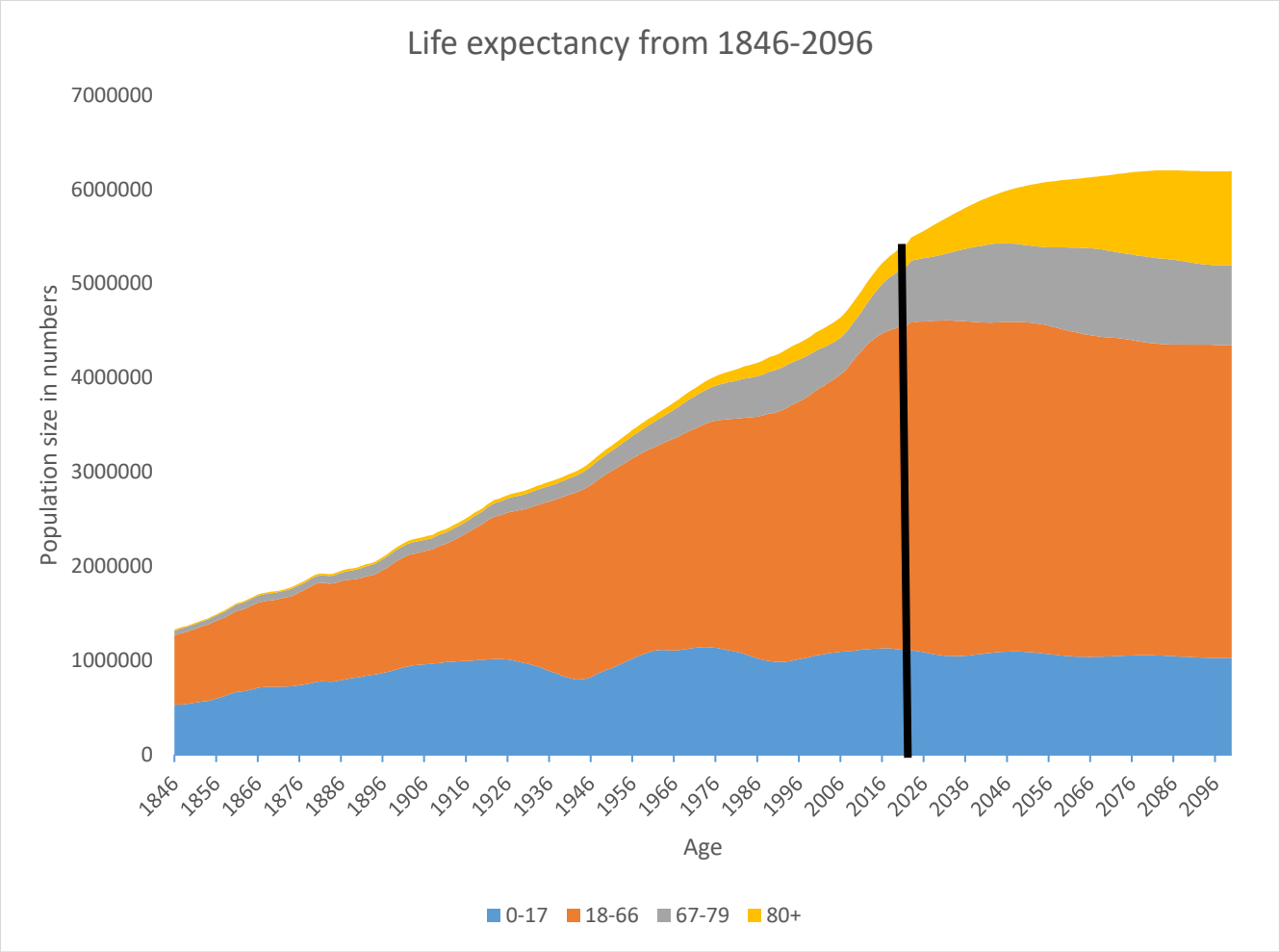


Figure 2: The population of Norway between the years 1846 to 2096, observed before 2022 and projected after. The numbers are collected from "Statistics Norway" tables 10211 and 13599. The projected numbers are using the main alternative of mean fertility, life expectancy and immigration (5, 6) Black line marks present time, year 2023.

As depicted in figure 2, the populations aged over 67 years of age are increasing notably, in contrast to the stagnant or potentially declining population within the most productive age range of 18 to 66 years of age. Nevertheless, this shift is accompanied by an upsurge in physical capacity (7, 8), suggesting a potential for improved physical health in later years. While this presents a promising outlook, there remains limited understanding of the cognitive health in older adults amidst this expanding lifespan. Will an extended life expectancy also provide years of cognitive vitality during the peaks of one's lifetime? Before addressing this question, it's imperative to elucidate certain concepts in the following paragraphs.

1.1 Cognition in healthy adults

1.1.1 Definition of cognition

Cognition describes the process of thinking - how we perceive, process and comprehend sensory input, and conduct ourselves correspondingly. This is analogous to a computer having four operations: input, storage, processing and output. Input is the brains ability to select, classify and integrate information, storage is its ability of memory and learning, processing is mental organization and reorganization of information, and expressive and executive function is the ability to act and communicate on information (9). A wordbook defines cognition as "a person's mental process of acquiring knowledge and understanding through thought, experience and senses" (10). The different operations are called cognitive modalities. This thesis will specifically address the modalities that were tested on the participants of the Tromsø Study, which will be elaborated upon in subsequent sections. Social cognition and behaviour will, due to this reason not be addressed. The modalities tested in the Tromsø Study are as follows:

- **Memory** is the brains ability to learn, store and retrieve information (9, 11). Memory has many subcategories, but can clinically be systemized as a dual main system, declarative and nondeclarative memory (9). The declarative memory holds the short-term memory including immediate memory and working memory. The information is "declared" in a conscious and intentional recollection process (9). Information retrieval differentiates between recall and recognition, where recall is a more complex process than recognition (9). Working memory is a part of the short-term memory and is described as a limited capacity system which allows the use and manipulation of information necessary for complex tasks and is a frontal lobe function (11, 12). Working memory is a bridge between short term memory, which lasts only 20-30 seconds, to long term memory, allowing previously acquired knowledge and experience to be connected to experiences in the present (9, 11). Integrating new information with existing knowledge enables the joint resolution of challenges or tasks. Long-term memory comprises both declarative and non-declarative components. The non-declarative aspect encompasses skills and knowledge retrieved and expressed without the subject's awareness, for example involving automated behaviours like riding a bike or walking (9, 11). The declarative part contains facts, concepts, and word meaning (11).

- **Attention** is a heterogeneous set of cognitive processes which allow a person to successfully cope with a continuously changing external and internal environment while maintaining focus on tasks (11). It is both a voluntary and a reflex/automated process, where processing of information occurs, and is summed up by Koziol et al like this: "At its core, attention includes both perceptual and inhibitory processes – when one attends to one thing, one is refraining from attending to other things" (13). A Cochrane review divided attention into 5 domains when evaluating rehabilitation after a stroke: alertness (ability and readiness to respond), selective attention (focusing on one stimulus, while ignoring others), sustained attention (focusing over prolonged time), spatial attention (to detect and deploy attention in different directions) and divided attention (multitasking) (14).
- **Processing speed** describes the speed in which a person processes different information from their surroundings and acts correctly according to the result of the information (15). It is not a unitary construct, but involves multiple neural networks, including stimulus perception, decision making and planning, motor performance and performance evaluation (16).
- **Psychomotor speed** is the relationship between consciously wanting to move and physically moving (17), and the participant's speed of performing a motor response to a signal from the brain (18).
- **Visuospatial function** is the ability to recognize and name objects from sight (11). It is described as having three components; visual perception, construction and visual memory (9). Visuospatial construction describes the ability to see an object or picture as a set of parts and then to construct a replica of the original from these (19). Visuospatial function is often tested in cognitive examination.
- **Executive function** describes a complex set of cognitive functions used to solve a problem and/or execute a task (11). It consists of the ability to plan a future goal through strategic action planning, and goal achievement through the use of information available, thus executing the task (11).
- **Calculation** comprises of oral and written arithmetical operations, including processing of symbols, execution of calculating procedure and understanding of arithmetical knowledge and procedures (11).
- **Orientation** may refer to orientation of one's person, time and space (11). The testing of orientation of one's person, time and space is fundamental in cognitive testing, and is

commonly used for examining neurological and psychiatric status, and probably represents three different domains, both anatomically and cognitively (20).

Cognitive reserve

When studying cognitive aging, it is essential to present the concept of cognitive reserve. Even though it has been defined differently through time, a large consensus report by *Stern et al.* from 2020 concluded that the cognitive reserve is the adaptability of cognitive processes that helps explain differential susceptibilities of cognitive abilities or day-to-day function to brain aging, pathology or insult (21), meaning brain's capacity to cope with different types of damage while maintaining the same cognition. Cognitive reserve is usually assessed by education level, but also job position, leisure time participation in cognitively and socially stimulating activities and verbal cognition (22, 23).

1.1.2 Epidemiology and history

The longevity of the Norwegian population is increasing (Figure 2), and citizens older than 70 years constituting 13% of the population in 2022 are expected to increase to 22% in less than 40 years, and by 2065 the amount of people in Norway over the age of 70 will have doubled (2). The demographic aged over 80 years constitutes substantial users of health services, and their numbers are projected to triple by the year 2065 (2). This implies that the total dependency ratio increases from 0,7 to 0,9 by 2060, approaching one-to-one ratio between the number of providers and the number needing support (2). This development will have significant consequences for the planning and providing care and health services in the future, as well as the impact on economics.

As a result of the shift in demographics to an elder population (Figure 1), there is an increasing focus on successful aging, including cognitive health (24). Alzheimer's Disease and cancer are the two most feared diseases (25, 26). However, cognitive decline is also associated with increased morbidity, mortality, and poorer quality of life (27, 28). This means that to address successful aging, we need to expand our understanding of cognitive health and disease. This will benefit both individuals, and society at large.

An interesting observation demonstrates that intelligence and cognition has been improving in adults over the last century and is often called the "Flynn Effect" (29-31). Historical evidence is based on young men around the age of 18 in several European countries, as tests of mental capability were usually performed on conscripts at start of military service. Flynn released a study that showed massive gain in IQ in 14 European nations, dating from the 1950s and three to four decades forwards (30). This effect was also shown later in low income countries such as Kenya, Sudan, and Turkey (32). The gain in IQ-tests has been explained by improved nutrition and health care, measured by the increasing height of young males as proxy (33, 34). It has also been suggested that the industrial revolution forced people to think in a more scientific way, thus developing skills suitable for mastering intelligence testing. With the industrial revolution came birth control, allowing fewer heads per household (35). Furthermore, the rise in education levels has probably also had a substantial impact on cognition, and this in turn, lead to increased cognitive reserve capacity (21). However, since the 1970s the cognitive gain slowed, until reaching a full stop in the mid-1990s. The Flynn effect plateau in Norway is mainly explained by an increasing number of low IQ scores (34). The negative Flynn-effect is also described in other countries such as France, Denmark, Finland, Britain, Netherlands and Estonia, even though it continues to rise in USA (36). The reason for this plateau effect is not yet known, but it is presumed that the effects of the industrial revolution, improved nutrition and health care, and even education, had reached their potential.

The Flynn effect theory is based mainly on young, male adults. Fewer studies have been done on middle aged and older adults, including women, and none have been conducted in Norway.

1.2 Dementia

"Dementia is a disease consisting in a paralysis of the spirit characterized by abolition of the reasoning faculty"

- *French Encyclopaedia (Diderot and D'Alembert, 1765) - (37)*

"There is no crime when the accused is in a state of dementia at the time of the alleged act".

- *Article 10 of the Napoleonic code - (37)*

1.2.1. History

Literature shows evidence of dementia-like cases, as far back as to the Old Testament; "Be kind to your father, even if his mind fails him" (38). In Roman times, the word dementia meant "being out of one's mind" and was used as a synonym for madness (37). The term was imbedded in legal documents from the 17th and 18th century, describing contracts and criminal acts that included people with dementia that could not be held accountable for their actions (37, 39). Its clinical significance varied across different literature, but it was at this time described as a type of madness, different from other states such as mania or delirium (37). The breakthrough in the understanding of dementia, occurred with the discovery of Alzheimer's disease, the most prevalent subtype of dementia.

The discovery of Alzheimer's disease in 1906 by Alois Alzheimer was not given the attention in the scientific community that it deserved. He discovered neurofibrillary tangles in the brain of his patient, Auguste Deter, a 55-year-old woman with severe dementia symptoms, and published his findings in 1907 (40). Few studies of Alzheimer's disease were performed over the next decades. It was presumed not to be the same disease as senile dementia, which at the time was described as a symptom of normal ageing. In 1976 German neuroscientist Robert Katzman was among the first to acknowledge Alzheimer's disease and senile dementia as the same disease in his paper: "The prevalence and malignancy of Alzheimer disease. A major killer" (41). Thus, Alzheimer's disease rose from a peculiar and rare disease to the fifth most common disease

overnight. In the last three decades extensive research has been done, on pathophysiology and disease modifying agents, revealing several pathways and subtypes of Alzheimer's disease, and yet no cure.

The awareness of cerebrovascular causes of dementia emerged in the beginning of the 19th century, with several descriptions of a "soft brain" and "hard vessels" in some people suffering from cognitive failure (37). By 1910 there was a subclass of dementia called "mental disorders with cerebral arteriosclerosis". Another psychiatrist living in Alois Alzheimer's time was dr. Binswanger, who presented his concept on vascular dementia in 1894 (42). He described a patient in his late forties presenting with dizziness, followed by a condition resembling a stroke. Over the next 4 years he developed symptoms like nocturnal confusion and aggression, increasing cognitive deficits, rubbing of hands and feet and two general seizures. After the patient's death dr. Binswanger found widespread large artery arteriosclerosis affecting the brain and other organs thus giving origin to Binswanger's disease, and an arteriosclerotic pathway to dementia. Alois Alzheimer's teacher Emil Kraepelin wrote the textbook "Psychiatrie" in 1896, in which he introduced the term atherosclerotic dementia based on the work of Binswanger and Alzheimer (43).

Frontotemporal dementia was first described as a dementia originating from the temporal lobe by the man who would get the disease named after him, Arnold Pick, in 1892 (37). In 1892 he described a 71 year old man who suffered from a failing mind and progressive failing language (44) He described an asymmetrical atrophy, different from the global atrophy seen in other dementias. In 1911 Alois Alzheimer confirmed these findings, and found the Pick Bodies (neuronal inclusions) (44). Between the years 1892 and 1906 Pick published 5 inaugural publications on brain atrophy and cognitive outcome (45).

As German psychiatrists rocked dementia research, a German neurologist (however, a son of a German psychiatrist) discovered an abnormal protein that disrupted the brains normal functioning in people with Parkinson disease, the protein Lewy body (46). The neurologist was called Friedrich H. Lewy, and his research gave the origin to the Lewy body protein, which causes dementia in Parkinson and Lewy body dementia.

1.2.2. Dementia today

Today we know that dementia is an umbrella term for several neurodegenerative diseases, as listed below. All dementia causing diseases are progressive, affecting cognition and behavior, as well as interfering with a person's ability to maintain the activities of daily living (ADL) (47). All dementia types exhibit an extended preclinical phase which is asymptomatic, though with underlying pathology which could lead to symptoms of dementia (48-52). Studies have demonstrated the presence of Alzheimer's disease pathology in brains up to 20-30 years before the onset of dementia (53, 54). Sequentially, the person may experience a subtle cognitive decline, not measurable in standard cognitive test batteries, so called subjective cognitive decline (SCI), as mentioned in National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines (51, 55, 56). SCI does not have a specific diagnosis code in ICD system. Nevertheless, SCI increases risk of detectable mild cognitive impairment (MCI) at a later point (56-58).

When a person becomes dependent on help to manage ADL, in addition to having cognitive impairment, the next stage, dementia, has occurred. Dementia is further sub-divided into mild, moderate and severe, according to the degree of neurocognitive and functional impairment, and its impact on ADL (59). WHO defines dementia in ICD-11 (59), by these 6 criteria:

- impaired cognition in two or more cognitive domains
- memory impairment as in most dementia forms
- neurocognitive impairment is based on both testing and information from patient, informant or observations
- behavior changes
- the cognitive change is not explained by other conditions.
- there must be an impact on ADL (59)

Subtypes of dementia, a short overview

- **Alzheimer's dementia**: Alzheimer's disease contributes to 60-70% of all dementia cases globally (60). Its pathophysiology is characterized by abnormal extracellular accumulation of β-amyloid plaque, deemed toxic to the brain, disrupting various neurotransmitters (61-63). Additionally, intracellular tau protein contributes to neurofibrillary tangles when released to synapses in neurons, causing disturbances in postsynaptic transfer and processing (61, 64). While the exact mechanism linking tau and β-amyloid plaque to Alzheimer's disease remains unclear, emerging evidence suggests a neuroimmune axis, possibly triggered by the plaques (65).
- **Vascular dementia:** Accounts for 15-20% of all dementia (66, 67). This dementia subtype is caused by vascular components such as ischemic or hemorrhagic acute cerebral events, atherosclerosis, small vessel disease, lacunar infarction, and amyloid angiopathy (67). Additional pathologies are cerebral hypoperfusion, oxidative stress and inflammation, endothelial dysfunction, and blood–brain barrier disruption (68). Symptoms vary based on the location of neurovascular damage, with common manifestations including deficits in attention, information processing, and executive function (66). It may have a more abrupt onset following acute cerebral neurovascular events, leading to a higher mortality rate (67).
- **Lewy body dementia and Parkinson's disease dementia:** These two types of dementia share pathology involving abnormal deposits of α-synuclein, known as Lewy bodies, in the brain. Symptoms encompass hallucinations, fluctuations in cognition, extrapyramidal motor impairment, Rapid Eye Movement (REM) sleep disturbance, and neuropsychiatric symptoms (69). In Lewy body dementia, the cognitive symptoms present before motor symptoms, while in Parkinson's disease, motor symptoms precede dementia by at least a year (70, 71).
- **Frontotemporal dementia:** It is caused by progressive atrophy of the frontal and temporal lobes (72). The symptoms include social dysfunction, personality changes, impairment in language, executive and motor symptoms (73). It is a common early onset dementia with an estimated lifetime risk of 1 in 742, but prevalence increases after the age of 65 (74). It exhibits high heritability, with around 30% having a strong family history of frontotemporal dementia (75).

- **Other specified forms of dementia:** Include alcohol related dementia (76), dementia in Huntington's disease (77), Creutzfeldt Jacobs disease (78), and progressive supranuclear palsy (73).
- **Multifactorial pathology of dementia:** Advances in understanding the neuropathology of dementia highlight a multifactorial aetiology, particularly in elderly individuals (11, 60, 67).

1.2.3. Epidemiology

Dementia is causing disability and cognitive decline in about 5% of the world's elderly population (79). By 2019, the prevalence was 57.4 million people, according to the "Global Burden of Disease Study 2019 (80). Prevalence of dementia is rapidly rising as longevity increases due to improved health care and decreased mortality in younger ages. Hence, prevalence of dementia is expected to triple by 2050 (79-83). Prevalence of dementia in Norway is higher than in comparable countries according to a study from 2020 (82). The cause of the heightened prevalence of dementia remains elusive but may potentially be attributed to increased longevity, or an elevated incidence. Estimated yearly incidence rates are reported to be about 9.9 million cases, of which Europe accounts for 25%, with a peak incidence in the ages 80-89 (79). Meanwhile, an increasing body of evidence suggests that the incidence of dementia is declining in western countries (80, 84-86).

Scandinavian studies (87-90) have confirmed the incidence decline, but studies of incidence over time in Norway are lacking. Knowledge on future incidence and prevalence of dementia is important for planning of health care resources and enabling health care systems to provide the best care and treatment for people with dementia and their families.

1.2.4. Treatment

Thus far, there has been a lack of curative or disease-modifying medications for Alzheimer's disease. However, in June 2021, the United States' Food and Drug Administration (FDA) approved the first drug targeting β-amyloid plaque, aducanumab a monoclonal antibody (91). Although the drug showed promise, it failed to gain approval from the European Medicines Agency later that year. The rejection was attributed to insufficient evidence of clinical improvement, high cost, and an unfavourable risk profile (91). More optimistic results have been

found for donanemab, another monoclonal antibody drug (92), demonstrating significantly slowed clinical progression in early Alzheimer's disease after 76 weeks. Nonetheless, the drug's risk profile, similarly here characterised by potential for brain oedema and microbleeds, raises considerable concern (92, 93). The approval process for this drug is still pending.

A third monoclonal antibody drug is lecanemab (94). FDA has approved the medication, but the use in Europe has not yet been decided (95). Donanemab and lecanemab do not target preclinical or late Alzheimer's disease (92, 94), and will probably not influence incidence nor prevalence significantly. Currently there are 36 drugs in phase 3 clinical trials targeting Alzheimer's disease (96), most targeting neurotransmitters and receptors in the brain.

The number of trials addressing vascular cognitive impairment in comparison to Alzheimer's is notably limited, with only nine phase 3 studies identified as of 2022 (68). Similar numbers are found for Lewy Body dementia with seven phase 3 studies in the same time period (97). The imperative for preventive measures across all forms of dementia remains crucial.

1.3 Risk factors for cognitive decline and dementia

In the absence of a cure for dementia, it is crucial to focus on prevention of dementia, prioritizing risk factors known to accelerate cognitive decline and dementia (81). Given that aging is the greatest risk factor for cognitive decline and dementia (81), and considering the global trend of improved longevity, an increasing number of individuals are being exposed to age as a risk factor for an extended time period. Hence, it becomes crucial to focus on modifiable risk factors.

Nine modifiable risk factors for cognitive decline and dementia were identified in a commission report from 2017 (98), and were later updated to twelve in 2020 (81) (Figure 3).

Figure 3: Population attributable fraction of potentially modifiable risk factors for dementia

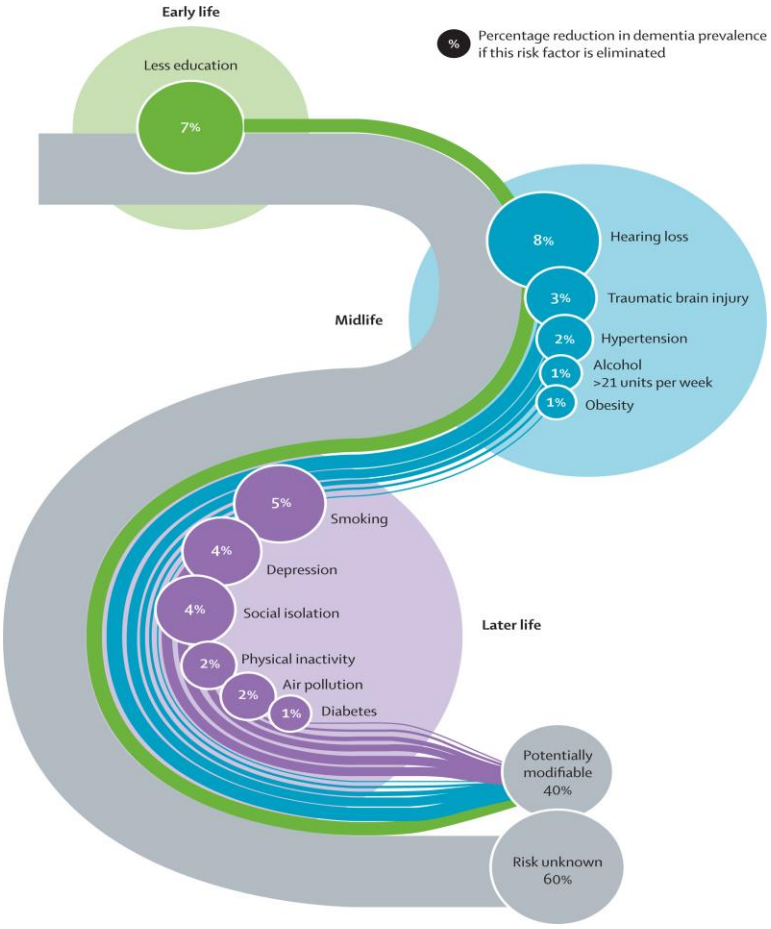


Figure 3: With licence agreement: The Lancet 2020 396413-446 DOI: (10.1016/S0140-6736(20)30367-6), Copyright © 2020 Elsevier Ltd. Percentage reduction in dementia prevalence if this risk factor is eliminated at different stages of life.

Many of the risk factors listed in Figure 3 have improved over the latest decade (8, 81, 99-101), especially increased education level, one of the most promising protective factors for cognitive decline (81). The improvement of risk factors has been suggested to explain the observed decline in age-specific incidence of dementia, particularly in high-income countries (85). It is worth noting that, as of now, no such studies have been conducted in Norway.

The following section will discuss some of the mentioned factors influencing cognition and the risk of dementia, and their trajectories over time in the population.

1.3.1 Physical activity (PA)

The Dementia Commission Report concluded PA to be an important factor to improve cognitive reserve capacity (81), and inactivity was suggested to account for 3% of dementia cases in 2017 (98) and 2% in 2020 (81). Previous research from the Tromsø Study indicated a U-shaped trend in leisure-time physical activity over the past four decades, with a notable increase in the last 20 years across all age groups (8). Simultaneously, occupational PA has shown a decline (102). The evidence regarding the association between PA and dementia is heterogeneous. While numerous observation studies suggest a preventive effect of PA on dementia (103, 104), several trials have attempted to test the association. However, as for now, no proven effect on cognition in dementia patients has been established in randomized controlled trials (105, 106). Nevertheless, a positive association has been observed between cardiorespiratory fitness and cognition in healthy adults, in both the FINGER study in Finland and in Norwegian studies (107, 108). The precise biological mechanisms through which PA affects cognition remain uncertain but are likely multifactorial. PA is proposed to influence the brain through exercise-induced circulating substances like Brain-Derived Neurotrophic Factor (BDNF), irisin and lactate (109, 110). Additionally, PA has shown to improve brain plasticity and support cognitive function (110). Some studies even suggested a long-lasting effect through changes to epigenetics by methylation, histone modification and microRNA alterations (110, 111). Moreover, an effect of PA on age-related hippocampal atrophy measured by MRI was observed, indicating a potential delay of atrophy by one or two years for active people, but the evidence for clinical effect was low (112). It is worth noting that the follow-up period for this study was limited to one year, thus possible delayed effects could not be ruled out.

It is noteworthy that the risk of dementia appears to be more pronounced with shorter follow-up time (113). One study found PA-levels to decrease up to nine years before onset dementia (114), suggesting a potential reverse causality.

1.3.2 Education

Education levels in Norway have increased over the last decades, as shown in Figure 4, and even over the last century (115).

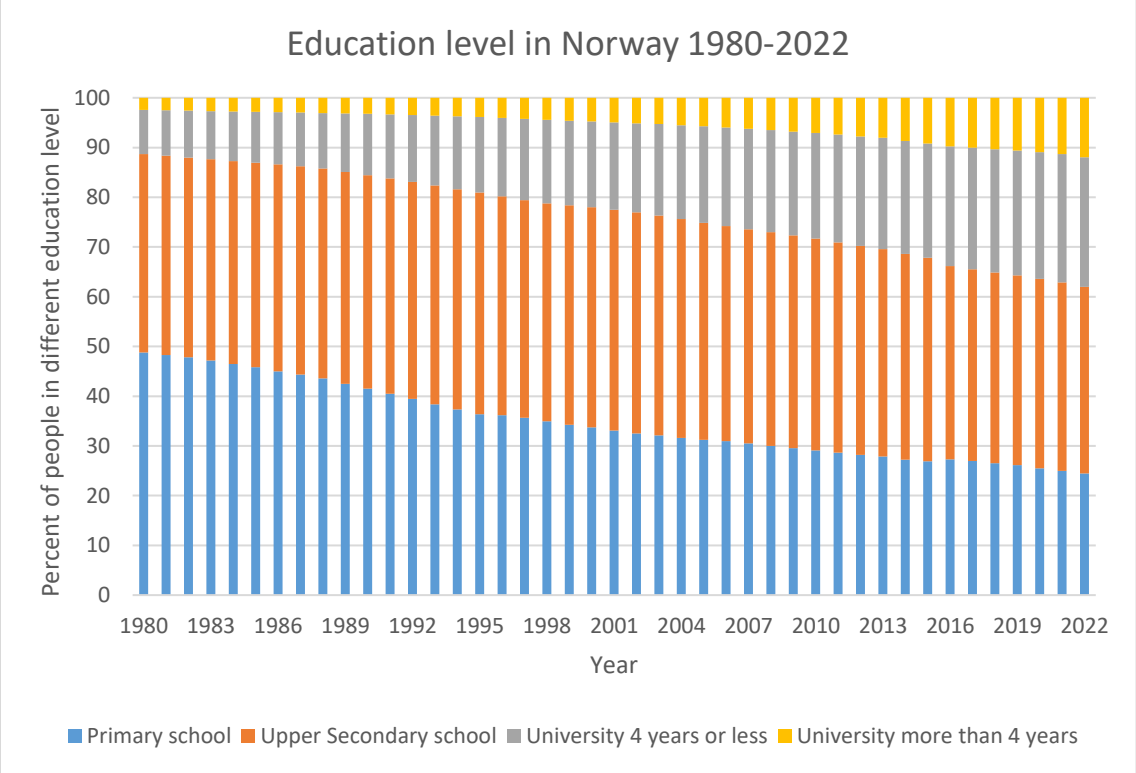


Figure 4: Education in the population of Norway over the age of 16, from 1980-2022. Graph made with data from Statistics Norway, table 08921 (116)

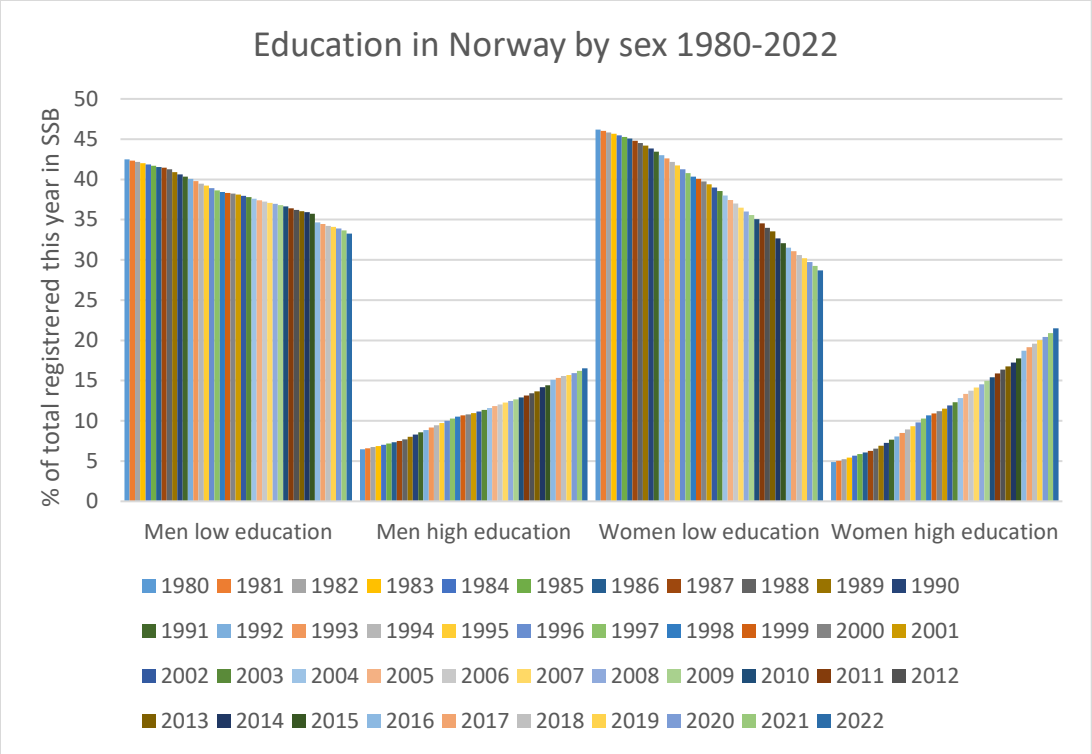


Figure 5: Y-axis: Percent of total both sexes each year. X-Axis: Groups of sex and education level. Low education: Primary school and upper secondary school. High Education: Primary, upper and university schooling. Graph made with data from Statistics Norway, table 08921containing the Norwegian population as a whole. N in 1980=3 091 689, increasing annually to 2022 when n=4 341 886 (116)

The increase in education level over the last four decades has been more pronounced in Norwegian women (Figure 5). The first 3/4 of the 20th century, women were less educated than men (115), but during the last 50 years, women have not only reached the same education levels as men, but have even surpassed them (Figure 5).

Increased education is a substrate for cognitive improvement in the population. Increasing education levels might affect dementia incidence, as education improves cognitive reserve (CR) (98, 117, 118). Education emerges as a robust protective factor against dementia (98).

However, according to the CR theory (117), education is posited not as a direct protective factor but rather as a means of enhancing the brain's resilience to dementia pathology. This enhancement consequently results in postponing the onset of dementia symptoms. However, people with high education and later onset of dementia, have a steeper cognitive decline compared to lower education-groups (118). In observational studies education is therefore a proxy for CR (23). Moreover, education seems to increase cognitive abilities also in the dementia-free population (100, 118).

1.3.3 Cardiovascular risk factors:

Studies from the Tromsø Study and done in similar populations, have shown that cardiovascular risk factors have improved (98, 119). Blood pressure (120), cholesterol-levels, diabetes (121) and smoking prevalence are decreasing (99). The improvement in cardiovascular risk factors has yielded positive outcomes, reflected in the decreasing incidence of heart disease over the past decades (122). As heart and brain diseases share many risk factors, a concurrent reduction in stroke rates is also observed (123). Additionally, the influence of cerebral small vessel disease (CVSD) on risk for cognitive decline and stroke are well-established (124, 125). CVSD is the most common cause of vascular cognitive impairment and dementia (126). Currently studies on the prevalence of CSVD over time in Norway are lacking. The incidence of CVSD increases with age (125, 127), and shares common risk factors with other cardiovascular diseases, including hypertension, smoking, hyperlipidaemia and diabetes (124). Additionally, low education has been associated with a higher burden of CVSD as determined by radiology (128). As these risk factors are improving in the population, and age-adjusted stroke rates are decreasing over time (129), there is hope that also the incidence of CVSD will decline in the elderly population. Simultaneously, the prevalence of obesity is on the rise (102, 130), and the impact of obesity to brain health and dementia is not yet clear.

Several cardiovascular risk factors, such as blood pressure, body mass index and cholesterol, have a u-shaped association with dementia incidence and mortality (131, 132). This indicates that both high and low values increase risk of dementia and mortality, in the same matter as seen for PA mentioned earlier.

1.3.4 Social contact and living alone

A large meta-analysis from 2017 concluded that lifelong single and widowed people have an increased risk of dementia (133). Other studies have shown that it is not the marital status, but the feeling of loneliness that gives the increased risk for dementia (134). It has also been discussed whether loneliness in the years preceding dementia could be due to a preclinical/prodromal phase, were the person developing dementia is self-isolating (81). It is notable that in long-term studies of the effect of loneliness on dementia risk, there are few with a

longer than 10-year follow-up. However, a Swedish study with up to 20 years follow-up did find an association between the feeling of loneliness and Alzheimer's dementia development, but not for vascular dementia (135). They discussed the reverse causality theory and did sensitivity-testing by removing those developing dementia within 5 years, but this adjustment could not rule out the possibility of reverse causality, as the preclinical phase has been shown to be longer (1).

1.4 Knowledge gaps

- Is cognition still improving in later born birth cohorts? If so, why?
- What is the incidence of dementia in Norway?
- Does PA impact cognition, and if so, is there a difference in those that later develop dementia?

2 Aims of the thesis

Paper 1: To analyse cognitive function in older adults over time in the Tromsø Study from 2001 (Tromsø5) to 2015/2016 (Tromsø7).

Paper 2: To find age specific incidence of dementia.

Paper 3: To study a long-term association between physical activity, cognition and dementia.

3 Material and methods

3.1 The Tromsø study

Tromsø municipality is located in Northern Norway, above the Arctic Circle. It currently inhabits almost 78,000 people, with only 16% born in foreign countries. The population is mainly Caucasian and comparable to the rest of Norway, with both rural and urban settings (136). The Tromsø Study was initiated in 1974 with the intent to study the high mortality-rate for cardiovascular diseases in Norway (137). At the time, men had the highest prevalence of these diseases. Therefore, in the first survey of 1974 (Tromsø1), only men were included. After this, women were invited, and the purpose of the surveys was widened to include a variety of diseases of interest, including cancer, diabetes, dementia, lung disease, physical health, chronic pain and many more. Since 1974, six more surveys have been conducted, seven to eight years apart. The latest, Tromsø7 was conducted in 2015-2016, and Tromsø8 is planned for 2025/2026. Over 45 000 people have participated in this ongoing cohort study, with a high attendance rate of 65% or more (138). Total cohorts or specified samples of the population have been invited and re-invited. The seven surveys had the same general enrolment design (137, 139). Detailed information about inclusion and distribution has been described elsewhere (137, 139). Based on the population registry, a personal invitation was sent in mail. In Tromsø4-7 there was a further invitation to a more extensive second survey. Beginning with Tromsø5, cognitive testing was included.

3.2 Study sample

Study Sample of all three articles

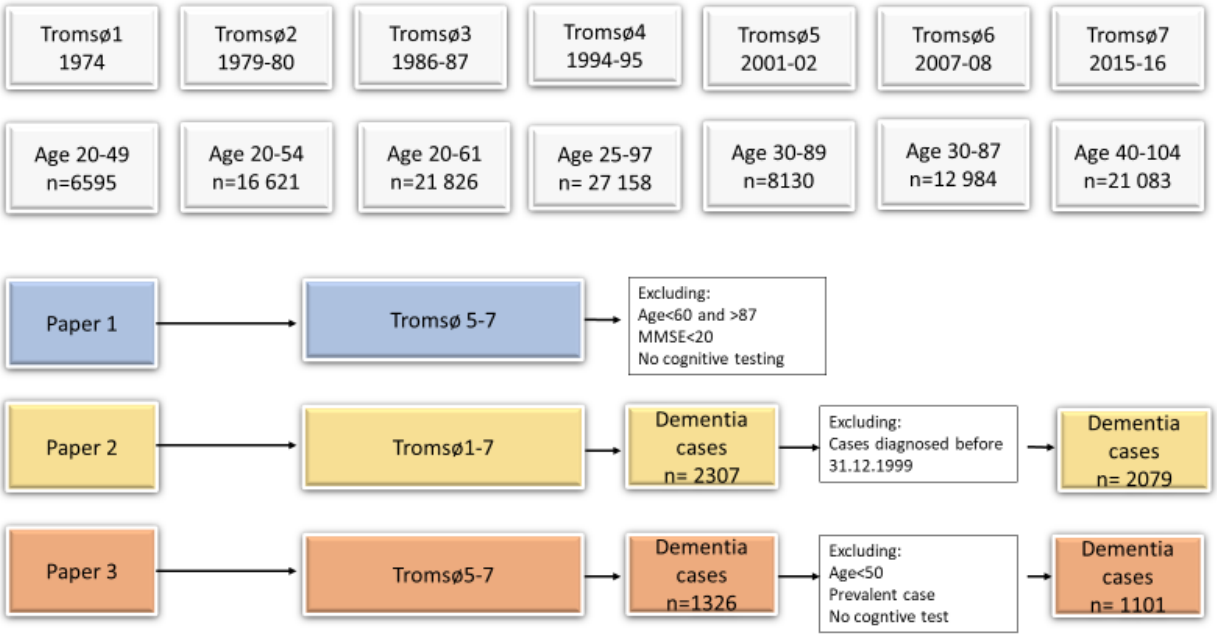


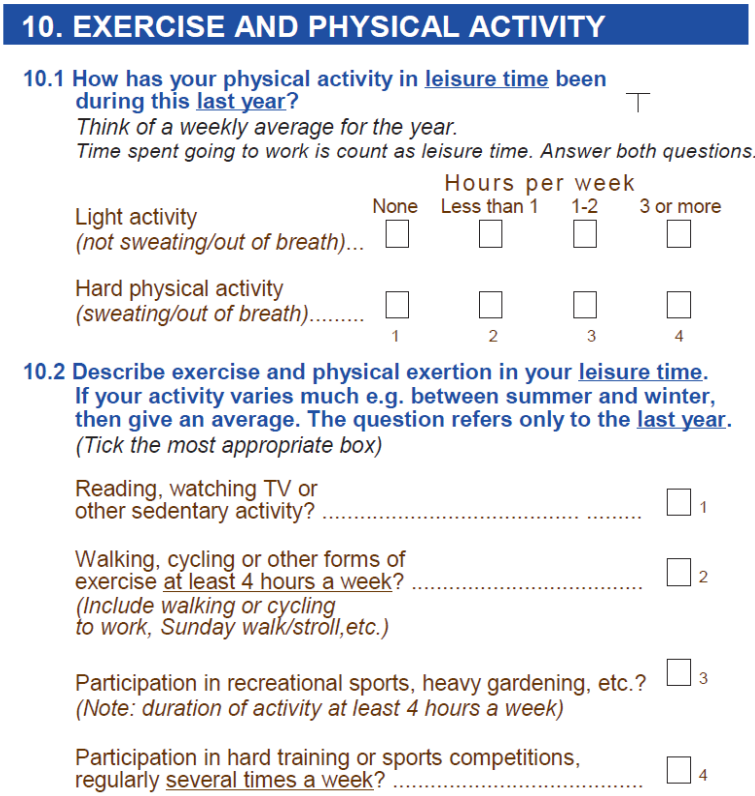
Figure 6: Flow chart of participants of The Tromsø Study, and inclusion in this thesis. Year of survey under the name of the survey (i.e., Tromsø1 – year 1974). Age is range of age of participant.

3.3 Collection of variables from the Tromsø Study

All participants were given an extensive questionnaire at their inclusion visit to any of the Tromsø Study surveys. Data collection included a self-completed questionnaire about diseases of interest, lifestyle factors, medication, exercise, nutrition, education, work, social relationships and other relevant parameters. Blood pressure and pulse were measured according to a standardized protocol (101). Blood samples were collected for analysis. For paper 1 and 3 we used serum total cholesterol, low density lipoprotein and high-density lipoprotein. A pre-defined, randomly selected sub-sample of participants were invited for a second visit in each wave, where cognitive testing was performed.

The covariates used in this thesis will be listed below, with a more extensive description of **physical activity** first:

Questionnaire PA from The Tromsø Study



10. EXERCISE AND PHYSICAL ACTIVITY

10.1 How has your physical activity in leisure time been during this last year?
Think of a weekly average for the year.
Time spent going to work is count as leisure time. Answer both questions.

	Hours per week			
	None	Less than 1	1-2	3 or more
Light activity *(not sweating/out of breath)...*	☐	☐	☐	☐
Hard physical activity *(sweating/out of breath).....*	☐ 1	☐ 2	☐ 3	☐ 4

10.2 Describe exercise and physical exertion in your leisure time. If your activity varies much e.g. between summer and winter, then give an average. The question refers only to the last year.
(Tick the most appropriate box)

Reading, watching TV or other sedentary activity? ..... ☐ 1

Walking, cycling or other forms of exercise at least 4 hours a week? ..... ☐ 2
(Include walking or cycling to work, Sunday walk/stroll,etc.)

Participation in recreational sports, heavy gardening, etc.? ☐ 3
(Note: duration of activity at least 4 hours a week)

Participation in hard training or sports competitions, regularly several times a week? ..... ☐ 4

Question 10.1 was asked solely in Tromsø4, and in Tromsø5 to those over the age of 70.

Question 10.2 was asked in Tromsø1-3, Tromsø5 under the age of 70, and Tromsø6-7. This question corresponds to the Saltin-Grimby Physical Activity Level (see below).

Figure 7: Picture on the left is cut from the questionnaire in Tromsø5 (138)

In our study, we specifically focused on physical activity during leisure time (LTPA). We did not incorporate occupational physical activity, as it is leisure-time physical activity that has been suggested to offer protective benefits against dementia (81, 140). LTPA in Tromsø1–3 and Tromsø5–7 was measured with the Saltin-Grimby Physical Activity Level Scale (SGPALS) questionnaire (141, 142). SGPALS results have been thoroughly validated in the Tromsø Study with accelerometer and VO2max (maximum volume of O2), finding significant correlations with self-reported activity and measured activity (143). Intra-class correlation with accelerometer measurement coefficient was 0.62 (95% CI 0.51, 0.71) for women and 0.59 (95% CI 0.47, 0.69)

for men. For VO2max the intra-class correlation coefficient was 0.86 (95% CI 0.81, 0.90) for both sexes (143).

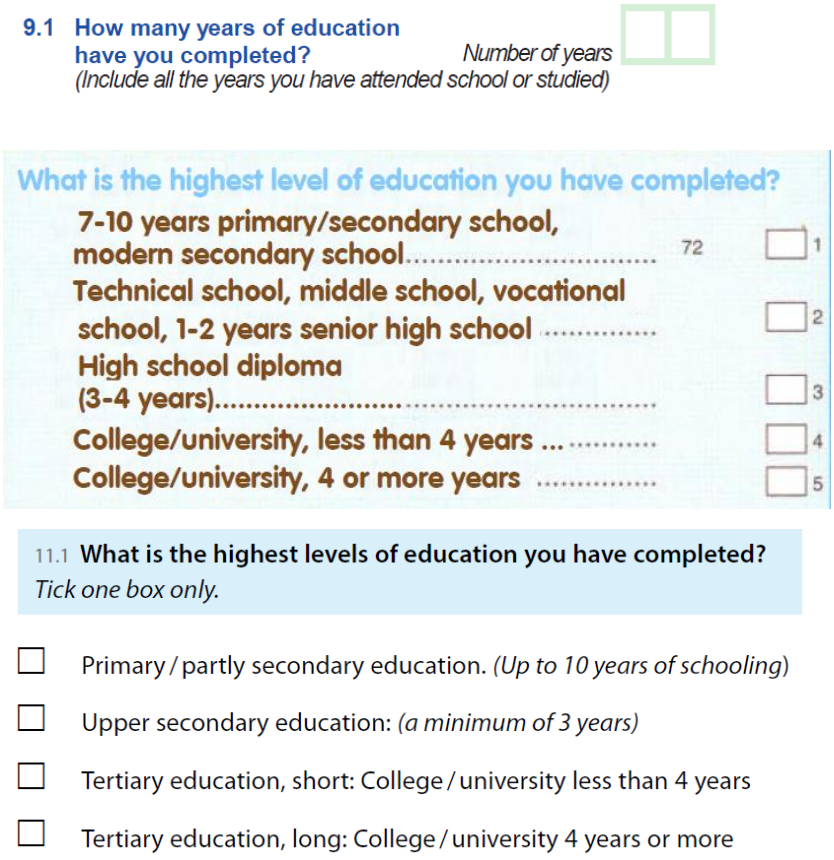
To minimize missing data in paper 3, we recoded SGPALS (Figure 7, question 10.2) and LTPA in light and hard activity (Figure 7, question 10.1) as a new, ordered categorical variable indicated by 0, 1, or 2, where 0 was inactive, 1 was active, and 2 was very active/athlete (see Appendix Table 1). Of the 25,124 in the study sample 21,177 had SGPALS and 25,058 had LTPA (66 missing). Correlation between these two variables was 0.97.

Sensitivity tests showed little difference in analysing SGPALS and the three categories of the new variable, and thus the latter variable was used in analysis.

Other variables:

- Blood pressure: The mean of the last two out of three measurements of systolic and diastolic blood pressure was used, following standardized procedure of all Tromsø Study surveys (101). High blood pressure was defined as systolic blood pressure over 140 mmHg, and/or diastolic blood pressure over 90 mmHg, and/or use of antihypertensive drugs.
- Hyperlipidaemia was measured with standardized method described elsewhere (99), as total serum cholesterol of 5 mmol/litre or more and/or high-density lipoprotein under 1 and/or use of lipid lowering drugs. We did not include low density lipoprotein as it was first introduced in Tromsø6 (2008).
- Diabetes, previous heart attack and previous stroke was extracted from self-reported data - yes/no, in all Tromsø Study surveys.
- Depression: for paper 1, self-reported questionnaire question “Have you in the last two weeks felt down/depressed?” was used with four alternative answers: “No”, “A little”, “A lot”, “Very much”. This variable was used as a categorical variable in the analysis.
- For paper 3, the Hopkins Symptom Check List-25 was used (see Appendix table e2) (144). This is a commonly used screening for psychiatric symptoms such as depression and anxiety. It consists of 25 questions, and score depression, anxiety and somatisation.
- Education was inquired about differently in separate surveys.

Questionnaire education from the Tromsø Study:



9.1 How many years of education have you completed? *Number of years*
(Include all the years you have attended school or studied)

What is the highest level of education you have completed?

7-10 years primary/secondary school, modern secondary school ..... 72 ☐ 1
Technical school, middle school, vocational school, 1-2 years senior high school ..... ☐ 2
High school diploma (3-4 years)..... ☐ 3
College/university, less than 4 years ..... ☐ 4
College/university, 4 or more years ..... ☐ 5

11.1 **What is the highest levels of education you have completed?**
Tick one box only.

☐ Primary / partly secondary education. *(Up to 10 years of schooling)*
☐ Upper secondary education: *(a minimum of 3 years)*
☐ Tertiary education, short: College / university less than 4 years
☐ Tertiary education, long: College / university 4 years or more

Figure 8: Picture on the left is cut from the questionnaire in Tromsø2-7 (138)

Tromsø2-3 and Tromsø5 asked for years of education.

Tromsø4 and Tromsø6 asked for five categories of education level.

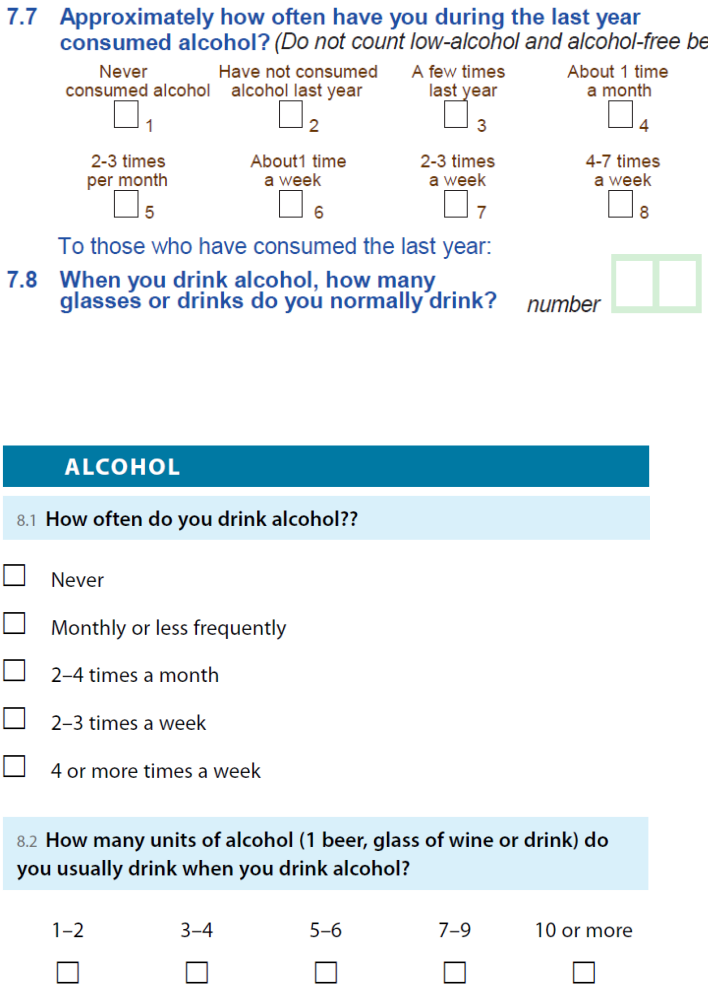
Tromsø7 also asked for categorical levels of education, but with only 4 categories.

Tromsø1 did not include information about education. We unified education variables by converting education level to the four categories used in Tromsø7. Tromsø4 and Tromsø6 asked for five categories of education level. The two alternatives "Technical school, middle school, vocational school, 1-2 years senior high school" and "High school diploma (3-4 years)" was used as one category called "Upper secondary school (at least 3 years)".

- Smoking in all Tromsø Study surveys was asked as "Do you/did you smoke daily?" Alternatives were "Yes", "Yes, previously" and "No, never".

- Alcohol use was asked in varying ways between the surveys. In the international recommendations and research units per week are often specified. Unfortunately, the questionnaires in The Tromsø Study did not include such an inquiry.

Questionnaire alcohol from the Tromsø Study:



7.7 Approximately how often have you during the last year consumed alcohol? *(Do not count low-alcohol and alcohol-free beer)*

Never consumed alcohol ☐ 1 | Have not consumed alcohol last year ☐ 2 | A few times last year ☐ 3 | About 1 time a month ☐ 4

2-3 times per month ☐ 5 | About1 time a week ☐ 6 | 2-3 times a week ☐ 7 | 4-7 times a week ☐ 8

To those who have consumed the last year:

7.8 When you drink alcohol, how many glasses or drinks do you normally drink? *number* ☐☐

ALCOHOL

8.1 **How often do you drink alcohol??**

- ☐ Never
- ☐ Monthly or less frequently
- ☐ 2–4 times a month
- ☐ 2–3 times a week
- ☐ 4 or more times a week

8.2 **How many units of alcohol (1 beer, glass of wine or drink) do you usually drink when you drink alcohol?**

1–2 ☐ | 3–4 ☐ | 5–6 ☐ | 7–9 ☐ | 10 or more ☐

Alcohol

On top: the questionnaire from Tromsø5. The number on units had variations from 0-70 units.

To the left bottom, questionnaire from Tromsø6-7

Figure 9: Picture on the left is cut from the questionnaire in Tromsø5-7 (138)

For paper 1, we only used Tromsø5-7 data about alcohol consumption – frequency and number of units, though questions differed as seen above.

We recoded the number written in units per occasion from Tromsø5 to the ordinal categories in Tromsø6-7 and did the same for frequency. “Not during the last year”, “A few times” and “1 time per month” was coded as “Monthly or less frequently”. “2-3 times per month”, and “1 time per week” were coded as “2-4 times a month”, and “1 time per month” and “2-3 times per

month" were recoded as "2-4 times a month". "Never", "2-3 times per week" and "4-7 times per week" was not changed. The units were not recoded to units per week as the difference in each category was too wide. Drinking 2-3 times per week and 3-4 units per occasion gave a range of 5-12 units/week in the same category, including both harmful and suggested non-harmful drinking in the same group, when cutoff was set to 7 units/week.

- Body Mass Index (BMI) was calculated using weight and height, which was measured in standardized ways at all seven surveys (102). The calculation was done by the formula:

$$BMI = \frac{Weight\ in\ kilograms}{(Height\ in\ cm)^2}$$

- Living alone variable was used in paper 3, as it has been proposed as a risk factor for dementia. All seven surveys included the question: "What is your marital status". Tromsø4-7 also included questions on whether one is living with other people than spouse/partner, such as children. If stated single and not living with other people, the participant was marked as "living alone".

3.4 Cognitive tests used in The Tromsø Study:

All cognitive tests were performed by trained personnel in a quiet office. The different cognitive tests evaluate different cognitive domains and describe cognition in both cognitively healthy participants and those with neurodegenerative disease. None of these tests are fit to use as a stand-alone tool to diagnose neurodegenerative disease (58, 145).

Word Test 1 – Immediate recall

Word Test 1 (WT1) is a 12-word memory test of short-term verbal memory (146). The participants were given two minutes to complete a free immediate recall of 12 nouns that were shown written on a board and read aloud at five-second intervals. One point was given for the correct recall of each word. Scores ranged from 0 to 12 (147, 148).

Word Test 2 – Delayed recognition

Word Test 2 (WT2) is a test of long-term verbal memory, episodic memory and the ability to use learning strategies (146). The 12 words from WT1 were shown and read aloud again mixed with

12 new nouns. The participants were asked to identify each word as new or known. One point was given for each word identified correctly. Points ranged from 0 to 24. (147, 148)

Digit Symbol Coding Test

The Digit Symbol Coding Test (DSCT) is part of the Wechsler Adult Intelligence Scale (149), and is used to examine perceptual processing, perceptual motor-speed, and memory (150). It is sensitive enough to reveal small changes in cognition, as it is influenced by psychomotor ability, sustained attention, processing speed, episodic memory and executive function (101). This test pairs nine numbers with nine symbols. Participants were asked to fill in as many correct symbols in numbered blank squares as they could in 90 seconds, without skipping a square. The number of correct symbols was the score of the test (146, 151).

Finger Tapping Test

In the Finger Tapping test (FTT), a test measuring psychomotor speed (152), the participants tapped their non-dominant index finger on a button for four 10-second rounds. The result was the mean tapping count of the last three rounds.

The Mini Mental State Examination (MMSE)

The Mini Mental State Examination (MMSE) is a widely used screening test for dementia, assessing global cognitive score (153). It consists of 30 questions and tasks, mapping the test subjects' cognitive function by a score between 0-30. However, as a test score under 24 implies cognitive decline, cognitively healthy people are differentiated by 6 points only, giving the test a ceiling effect.

MMSE was excluded from the analyses in paper 1 as it was first introduced in 2008, and we aimed to explore trends since 2001.

3.5 Dementia registry

An endpoint registry was made by retrieving all dementia diagnoses from hospital records in the University Hospital of North Norway, the sole hospital serving the region. Situated as the only hospital within a radius of 240 kilometres in one direction, and 300 kilometres in the other, it

functions as the primary healthcare centre for individuals requiring outpatient care or hospital admission for various medical conditions. Specialized dementia diagnostics are conducted in three departments of the University Hospital of North Norway: the neurological department, examining patients <65 years; the geriatric department, examining mainly patients ≥65 years, and the psychiatric department for older adults, addressing mainly dementia with neuropsychiatric symptoms. The registration of dementia diagnoses does not necessitate examination at this hospital; however, such diagnoses are often coded alongside other medical conditions. Consequently, individuals diagnosed with dementia by their general practitioners and subsequently referred to a specialist, will also be recorded in this registry. In the pilot described below, 11% had a dementia diagnosis in hospital records, but was evaluated and diagnosed firstly outside the specialized hospital departments, i.e., general practitioner or a surgical department.

All who had participated in any wave of the Tromsø Study, and later received a dementia diagnose, was included. The search extracted 33 082 diagnoses from the journal system, yielding 3552 unique participants. Dementia diagnoses were found in 2307 participants, with 279 participants receiving the diagnosis between 1. January 1986 and 31. December 1999.

We used ICD-codes from the "International Statistical Classification of Diseases and Related Health Problems" (ICD-10) coding for Alzheimer's disease, vascular dementia, Lewy body dementia, Parkinson dementia, and other specified and unspecified dementia diagnoses.

A validation was performed using 150 randomly selected patients, 50 from each five-years period from 2000-2015. Each patient was manually checked by reading the records to confirm the ICD-10 diagnosis. To validate our registry from 2016 to 2019, we merged it with an ongoing multicentre study, "The Norwegian registry of persons assessed for cognitive symptoms" (154), and were able to validate 255 diagnoses from 2016 to the end of 2019.

Interestingly, during the validation study we observed that in later time periods more cognitive tests were performed, more data on next of kin/family observation were documented, and more ADL and physical tests were included, compared to the first time period of 2000-2005. Another empirical observation was that somatic health care professionals documented more tests and more family information, than did psychiatric wards.

Table 1: ICD-10 codes used to extract dementia-diagnoses

ICD-10 codes	Diagnoses
G30·0	Alzheimer disease with early onset
G30·1	Alzheimer disease with late onset
G30·8	Other Alzheimer disease
G30·9	Alzheimer disease, unspecified
G31·8	Other specified degenerative diseases of nervous system including LBD
F00·0	Dementia in Alzheimer disease with early onset
F00·1	Dementia in Alzheimer disease with late onset
F00·2	Dementia in Alzheimer disease, atypical or mixed type
F00·9	Dementia in Alzheimer disease, unspecified
F01·0	Vascular dementia
F01·1	Multi-infarct dementia
F01·2	Subcortical vascular dementia
F01·3·	Mixed cortical and subcortical vascular dementia
F01·8	Other vascular dementia
F01·9	Vascular dementia, unspecified
F02·0	Dementia in Pick disease
F02·1	Dementia in Creutzfeldt-Jakob disease
F02·2	Dementia in Huntington disease
F02·3	Dementia in Parkinson disease
F02·4	Dementia in human immunodeficiency virus [HIV] disease
F02·8	Dementia in other specified diseases classified elsewhere
F03	Unspecified dementia

Table 1: ICD codes used for extraction of dementia diagnoses from the hospital journal system.

3.6 Ethics

The Tromsø Study is performed in accordance with the 1964 Helsinki declaration, and its later amendments. The studies in the thesis have been approved by The Regional Committee for Medical and Health Research Ethics (REK Nord, reference 2016/389). Written informed consent was given by all participants of The Tromsø Study.

3.7 Statistical analyses

All analyses were performed using Stata version 17.0; StataCorp College Station, Texas, USA.

Paper1

Data from Tromsø5-7 were pooled and analysed as one set. Firstly, to investigate whether cognitive test scores improved in later birth cohorts, we did a multiple linear regression analysis in different 7-year age-groups in subjects over 60 years of age, with the respective cognitive tests as the dependent variable and study wave as independent covariates. All models were adjusted for age and sex. Secondly, to investigate how much other covariates mediated the changes in test scores between study waves, covariates were added one by one in the whole age span (in the following order: age, education, blood pressure, hypercholesterolemia, smoking, stroke, previous heart attack, depression, diabetes, PA, alcohol units, alcohol frequency, height and BMI), and we investigated the change in percentage in the coefficient for the study wave. The interaction terms age*study-wave and study-wave*sex and sex*age and sex*age*study-wave were included to allow for different changes over time by sex and age. There were 2852 missing values in one or more of the covariates, which were adjusted with multiple imputation by chained equation. The imputation was based on the variables age, sex, study wave and the respective cognitive variable. The cognitive test scores were not imputed. All missing values of the mediators were below 3.5%, except for alcohol consumption (n=2707), depression (n=1099), and PA. PA in Tromsø 5 had a high missing rate (n=2852), as participants over 70 years of age (n=1615) were not asked a relevant question about PA.

Paper2

The Tromsø Study1-7 was linked to the dementia end-point registry. As we had few dementia cases (n = 279) before 2000, and we wanted to include only new cases (n = 2079), participants who had their first dementia diagnosis registered in the hospital records before 1 January 2000, were excluded. The diagnosis of dementia was dichotomized as yes/no. The baseline for follow-up was the first date of participation in any Tromsø Study survey. If the first diagnosis of dementia was established before baseline, the participant was excluded. The exit date was set to the date of the first dementia diagnosis in hospital journals, the date of death, date of moving out of the municipality, or the exit date 31. December 2019, whichever came first. The age at the start of the study was set at 1 July of the entry year minus the birthdate, divided by 365.25.

A new observation was generated for each participant every calendar year from 2000, including age, time in years, and dementia status. We then made 10-year age-groups from 50 years and older, and performed the following analysis on each age-group separately:

We used Poisson regression models to assess the association between calendar time and dementia incidence. Calendar time was modelled using fractional polynomials. The best-fitting model (out of 44 models) was determined using Akaike's information criterion (155). In separate Poisson models, calendar time was modelled as a categorical variable, with indicator variables for each calendar year. All models were adjusted for age (Figure 11 in results).

The incidence rate ratio was calculated by comparing the incidence in 2000 and the incidence in 2019 for each age group. To test for significant time trends, we used a likelihood ratio test that compared a model with and without calendar time (Table 3).

To control for a small number of cases in annual rates within some age groups, we combined calendar time into 5-year intervals, and calculated incidence rates per 1000 person-years with 95% confidence intervals (CI) for each time and age group.

Paper 3

As the various cognitive tests had different reference values, we standardized the scores by calculating z-scores for each test. Subsequently, we computed a global cognitive test score, by determining the mean z-score across all tests administered to each participant.

To visualize how education and PA were associated with cognitive scores, plots were constructed by calculating predictions for global cognitive function from a linear regression of global cognitive function on age. To measure effect size between the groups with dementia-free participants and those who later developed dementia, we used Hedge's g for LTPA and the global cognitive test score.

Considering the repeated measures design, multilevel mixed-effects linear regression was used to investigate the association between LTPA and cognitive abilities in those who later developed dementia, compared to those remaining dementia-free. Models were fitted using likelihood ratio tests. The time variable was calculated as time from participation in the Tromsø Study to dementia diagnosis, death or study exit (31.12.2019), whichever came first.

Moderators were added successively, always including the independent variables LTPA and age in the model.

We first constructed four models to see how different covariates affected the β-coefficients for activity, with global cognitive score as the outcome. The models were: Model 1: adjusted for age and time, Model 2: Model 1 + education, Model 3: full model, including Model 2, comorbidity and lifestyle factors. To see if different cognitive area (as described under cognitive tests) were affected differently by LTPA, we also ran a fourth model with Model 2 on all cognitive tests separately. Interaction was tested by including the interaction term with age and PA, time and LTPA, sex and LTPA, and education and sex.

Sensitivity testing was done by excluding those who scored low on the cognitive tests to see if participants with undiagnosed cognitive failure caused a lack of association between LTPA and cognitive test scores in those who later developed dementia. Participants with possible undiagnosed cognitive failure were excluded. We ran sensitivity tests, removing the lower 2,5 percentiles of scores, with no difference in significance and only small changes in beta values. However, number of dementia cases dropped from 1123 to 897.

4 Results

4.1 Paper 1:

“Improved Cognitive Function in the Tromsø Study in Norway From 2001 to 2016”

In this paper we included 5192 women and 4342 men. Mean age was 68.8 years, with a range of 60-87 years. For the four included cognitive tests, we found that test scores improved in later-born birth cohorts for all ages, and in both sexes, more so for men than women, adjusted for age. Combined, the increase in education, PA, alcohol intake and height, and decrease in smoking prevalence, in later born cohorts mediated, on average, 34.4% (range 24.5–47.7%) of the improvement between Tromsø5 and Tromsø7 in women’s results on the four cognitive tests, and 51.6% (range 35.8–73.4%) in men. The largest improvement was seen in the Digit Symbol Coding Test. All results were statistically significant over the level of 99%, except for the age-group 81-87 years, which did not reach statistical significance for men in Finger Tapping Test. To test for association with the known risk factors, we made a second model where we adjusted for age, education, blood pressure, hypercholesterolemia, smoking, alcohol units, alcohol frequency, previous stroke, previous heart attack, diabetes, depression, PA and body mass index. In this second model the results remained robust for all women’s age categories in all tests, but in the oldest men all four cognitive tests did not longer reach statistical significance. For men under the age of 80 the results remained robust also in the second model.

In the Digit Symbol Coding Test, the improvement for those born later corresponded to 12 years of age for women and 10 years of age for men, meaning that 70-72-years old in 2015/2016 performed on the same level as 60-year-olds in 2001. For Word Test 2 testing long-term verbal memory, episodic memory and learning strategies, we found 80 years old to be the new 60.

The improvement was positively associated with increased education level, increased PA, increased alcohol consumption frequency, but not increased units of alcohol. For men there was also a positive association with smoking cessation and increased height.

Cognitive scores in 2001 (green line) compared to 2015/2016 (red line)

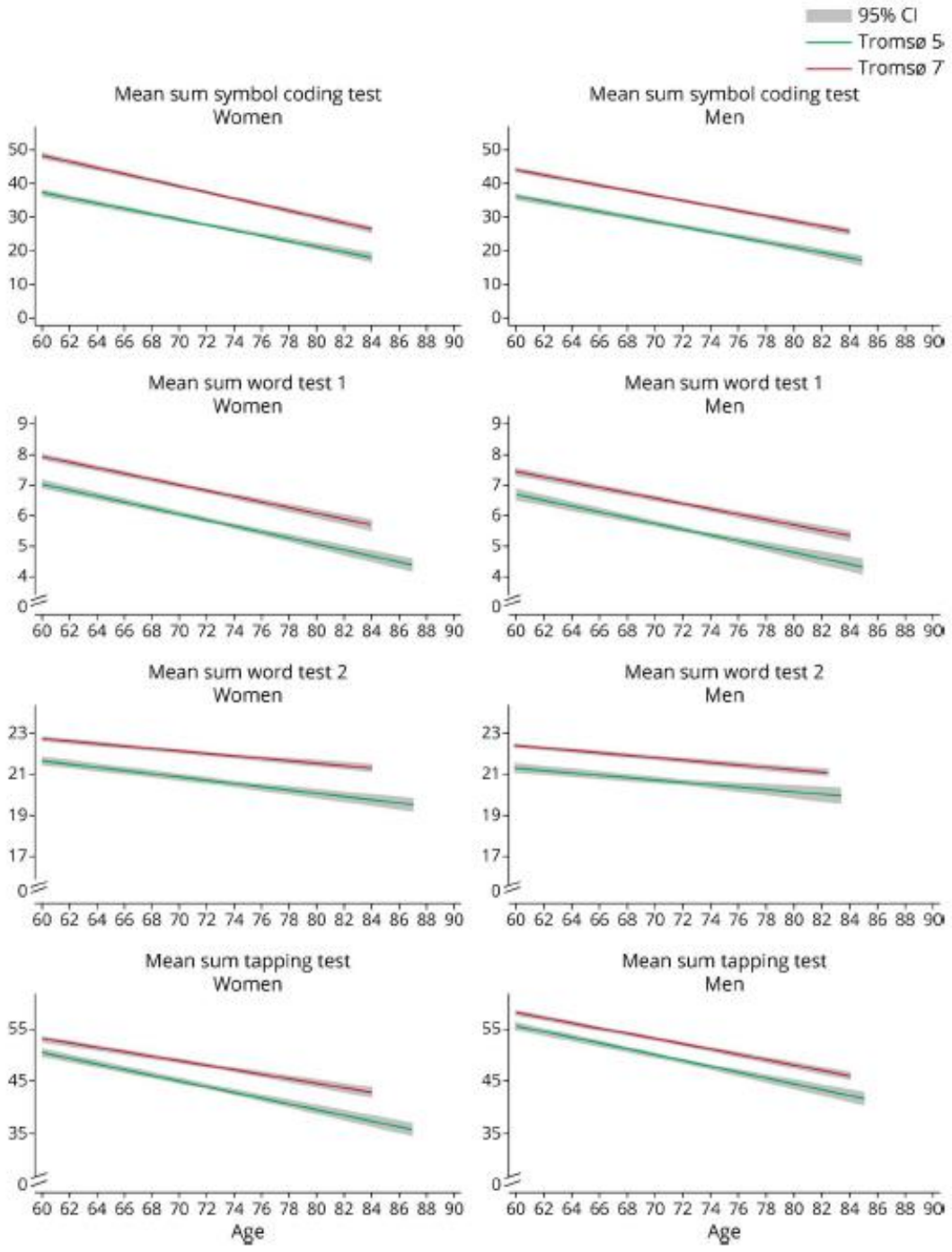


Figure 10: Differences of cognitive scores with 14/15 years apart. Estimation is done with linear regression with 95 % confidence interval marked with grey around each line. The y-axis is for three tests has included a scale brake, to better illustrate the age-specific improvement on time.

4.2 Paper 2:

"Incidence of dementia over a period of 20 years in a Norwegian population"

In paper 2 we included the entire population of Tromsø Study participants, a total of 44 411 individuals, who participated once or several times in Tromsø1-7. From this list, we extracted dementia diagnoses from The University Hospital of North Norway, the only hospital in the area. We found 2307 cases, of which 2079 (58% women) were diagnosed after 1.jan 2000.

The mean age at dementia diagnosis was 81.5 (95% CI, 81.0-82.0) years for women and 78.8 (95% CI, 78.3-79.3) for men. The number of person-years from year 2000 to the end of 2019 was 662 434. There were fewer men (n=874) than women (n=1205) who developed dementia. Those who later developed dementia, reported to be more inactive, had lower education level, more often had hypercholesterolemia, and hypertension before their diagnosis. Additionally, they reported more depression and anxiety symptoms (Hopkins symptom check list) prior to dementia.

We found that age-specific incidence of dementia had decreased by up to 61% over the last two decades. The trend was statistically significant in participants aged 60-99 years and was similar for both sexes. The analyses were done for 10-year age-groups with 198 720 person-years for 50-59 years old, 151 217 person-years for 60-69 years old, 77 564 person-years for 70-79 years old, 27 489 person-years for 80-89 years old, and 3586 person-years for those above 90 years old. Firstly, we analysed annual incidence rate per 1000 person-year and visualized this in graphs. This showed a decrease in incidence over the last two decades for participants in the ages 60-99. In the group 50-59 (n=44) the trend did not reach statistical significance. We then analysed incidence rates in five calendar-year groups, from 2000 to end of 2019, to include more cases in each group and to give results more power. This did not change the trend of decreasing incidence of dementia over the last two decades.

Incidence rate of dementia

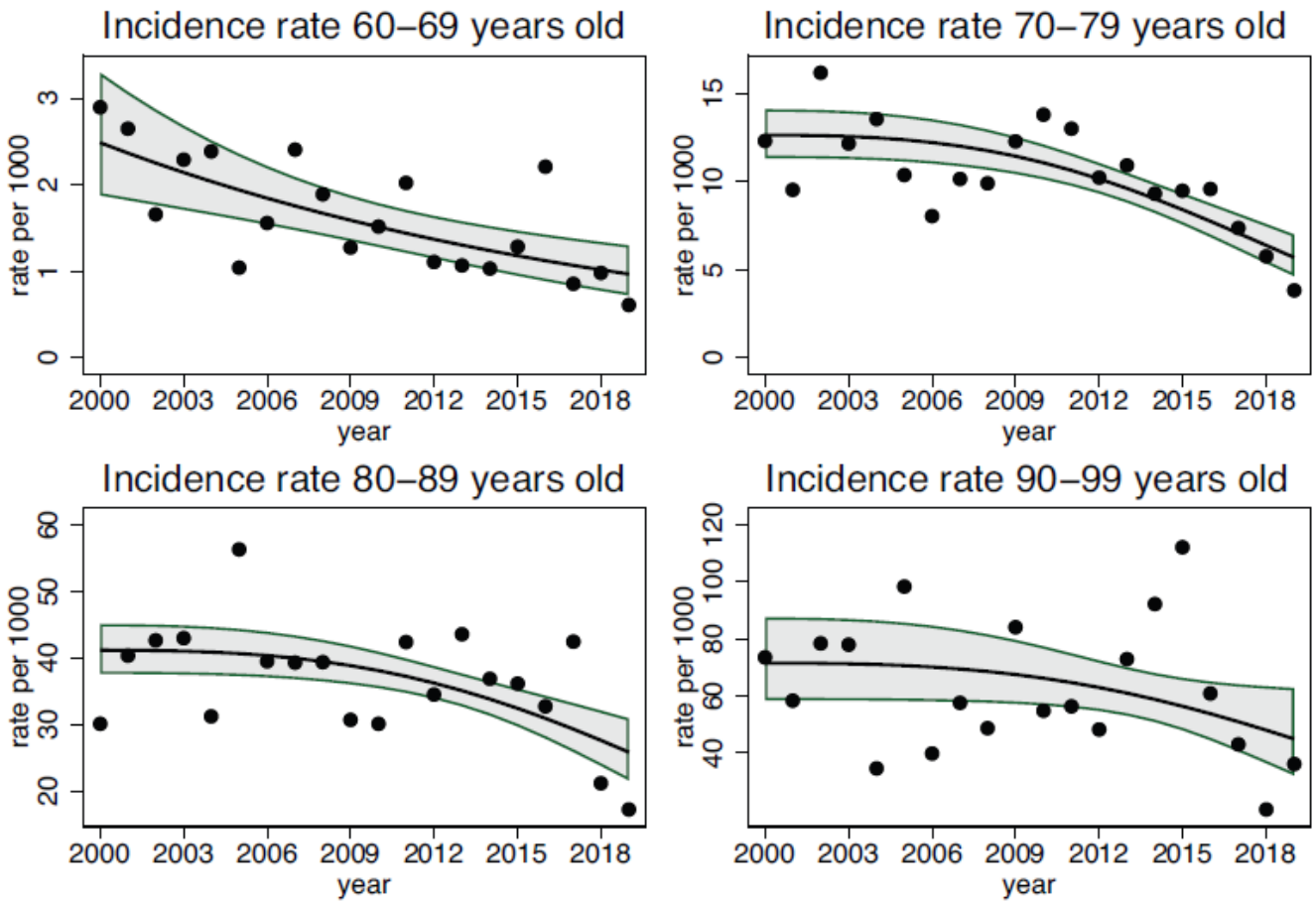


Figure 11: Incidence rate of dementia per 1000 in different 10-year groups over the last two decades

Five-year incidence rate per 1000 person-years by age group

Age group	*50-59*		*60-69*		*70-79*		*80-89*		*90-99*	
5-year group	*IR/1000*	*95% CI*	*IR/1000*	*95% CI*	*IR/1000*	*95% CI*	*IR/1000*	*95% CI*	*IR/1000*	*95% CI*
2000-2004	0.27	(0.14-0.52)	2.7	(2.1-3.6)	15.2	(13.1-17.5)	37.8	(32.8- 43.7)	63.5	(44.4-90)
2005-2009	0.26	(0.13-0.5)	1.4	(1.4-2.4)	12.0	(10.3-14.1)	41.4	(36.5-47.1)	63.9	(49.2-88)
2010-2014	0.2	(0.1-0.43)	1.2	(1.2-2.1)	12.7	(11.0-14.7)	39.4	(34.8-44.6)	66.4	(51.9-84.9)
2015-2019	0.32	(0.18-0.57)	1.1	(1.1-1.9)	7.7	(6.5-9.0)	30.1	(27.0-35.4)	52.8	(41.1-67.7)
Person years	139196		106049		58919		23531		3280	
IRR, 2000 vs 2019	1.0	(0.23-4.2)	0.39	(0.15-1.02)	0.45	(0.41-0.49)	0.88	(0.46-1.7)	0.63	(0.51-0.78)
Time-trend P-value	0.99		<0.001		<0.001		<0.001		0.04	

Table 2: Likelihood ratio test used to test for annual significant time-trends in the different age groups. IR – incidence rate, CI – confidence interval. IRR - incidence rate ratio between 2000 and 2019.

4.1 Paper 3:

“Leisure time Physical Activites’ association with cognition and dementia, a 19-year life course study”

In paper 3 we wanted to see how cognition and dementia was associated with PA. For this study we included 11,512 participants. They had all done at least one cognitive test in Tromsø5-7. We excluded all participants under 50 years old, as we wanted to see PA effect on middle-aged and older adults. Of these, 1123 later developed dementia (55% women). Those who had dementia diagnosis before inclusion in the study where excluded (n=22), leaving 1101 cases. Mean age at first participation in the Tromsø Study for subjects later developing dementia was 70.8 years, and for those remaining dementia free 61.8 years. Age range for first participation was 50-98 years. Maximum follow-up time was 19 years.

We found that leisure time physical activity (LTPA) was positively associated with global cognition only in those remaining dementia-free, and that the results were indifferent to the

choice of cognitive measurement. Interestingly, there was a widening cognitive score gap with increasing age among active and inactive participants in the dementia-free group, a phenomenon not evident in the group later developing dementia. For them, the trend curve of cognitive scores progressed similarly with age regardless of the activity level prior to dementia diagnosis.

Digit Symbol Coding test emerged as the most sensitive to cognitive change. This was the only test where LTPA exhibited a positive association with cognition in individuals later developing dementia. Among men in this group, the association was only present for the very active. Conversely, for women later developing dementia, there was a positive association in both active and very active group.

Short-term memory improvement was noted in women developing dementia; however, upon adjusting for education, this association disappeared. This suggests that education acts as a strong mediator, even in people in a preclinical phase of dementia. Notably, no association with short-term memory was observed in men.

Global cognitive scores in women and men.

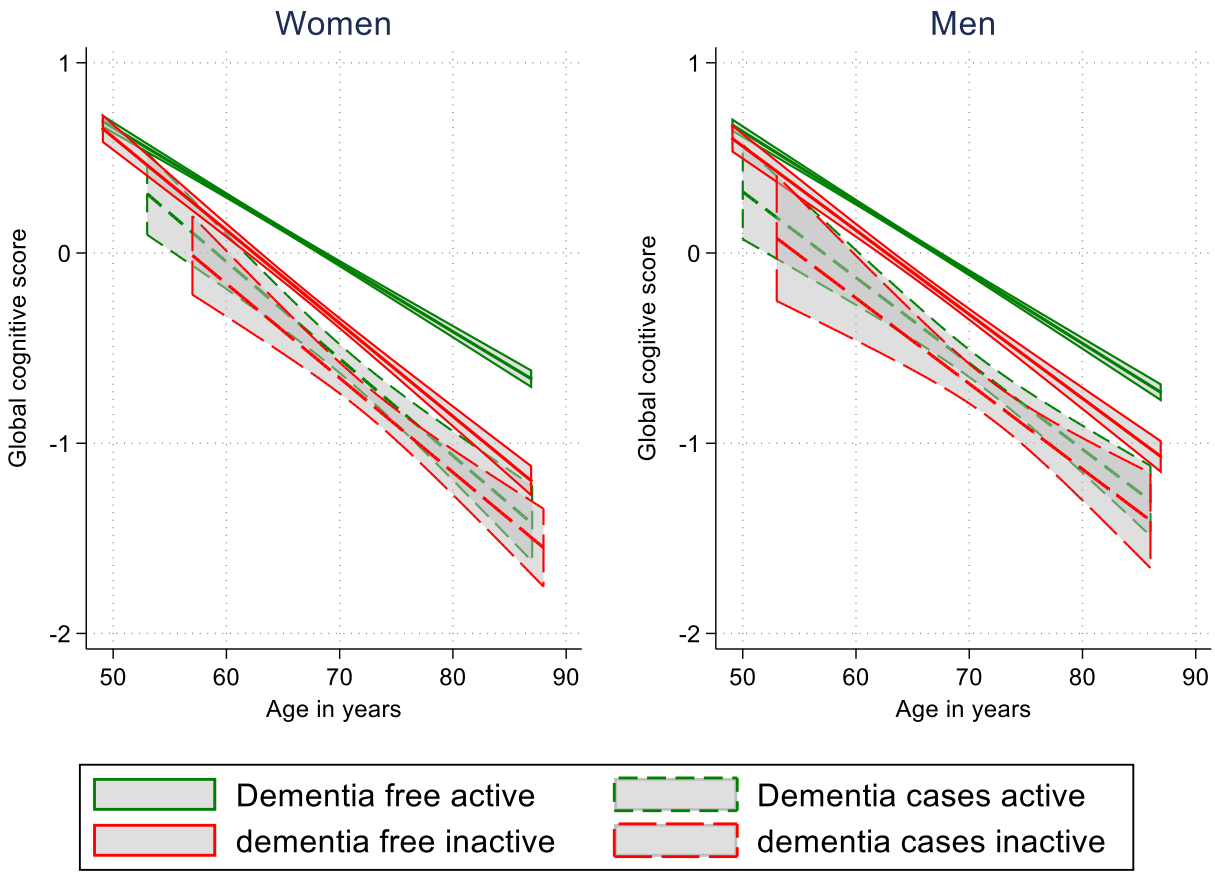


Figure 12: Linear fit prediction plot for global cognitive scores in women and men, grouped according to activity level and dementia.

Effect of physical activity on global cognitive score, mixed effects model

	Women				*Men*			
Z-values	***Dementia-free***		***Dementia cases***		***Dementia-free***		***Dementia cases***	
N	***5625***		***648***		***4764***		***454***	
Global CF	***β***	***CI 95%***	***β***	***CI 95%***	***β***	***CI 95%***	***β***	***CI 95%***
Model 1								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.15***	(0.0.12- 0.18)	0.04	(-0.07- 0.15)	0.12***	(0.09- 0.16)	0.03	(-0.09- 0.14)
Very active	0.18***	(0.13- 0.22)	0.26*	(0.06- 0.46)	0.15***	(0.11- 0.20)	0.09	(-0.07- 0.25)
ICC	0.0.536	. .	0.422	. .	0.528	. .	0.480	. .
Model 2								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.12***	(0.08- 0.15)	-0.01	(-0.12- 0.10)	0.10***	(0.07- 0.13)	0.02	(-0.10- 0.13)
Very active	0.11***	(0.07- 0.16)	0.17	(-0.03- 0.37)	0.11***	(0.07- 0.15)	0.05	(-0.11- 0.22)
ICC	0.495	. .	0.379	. .	0.464	. .	0.453	. .
Model 3								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.09***	(0.05- 0.12)	-0.05	(-0.17- 0.06)	0.08***	(0.04- 0.11)	0.02	(-0.10- 0.14)
Very active	0.08***	(0.03- 0.13)	0.14	(-0.08- 0.36)	0.07***	(0.03- 0.12)	0.02	(-0.15- 0.18)
ICC	0.482		0.328		0.446		0.522	

*Table 3: Multiple mixed linear regression with nested id and global cognitive test score outcome. Model 1: adjusted for time and age, Model 2: Model 1 + education, Model 3: Model 2 + comorbidity and lifestyle factors. ICC: Intra class correlation * p < 0.05, ***

5 Discussion

5.1 Main results of the thesis

- Cognitive test scores improve in later born birth cohorts in people over the age of 60 years old (paper 1).
- Women outperform men in three of four cognitive tests, and in global cognitive score (paper 1 and 3).
- 80-year-old people in 2015/2016 preformed as well as 60-year-olds in 2001 on cognitive tests (paper 3).
- Improved cognition in the common population is positively associated with increased education level, increased modest drinking frequency and increased physical activity. For men it is also explained by smoking cessation and increased height (paper 1).
- Dementia incidence is decreasing in the ages between 60-99 (paper 2).
- Leisure time physical activity is positively associated with increased cognitive test scores in those remaining dementia free (paper 3).
- For those later developing dementia, high physical activity before diagnosis did not improve cognitive test scores before dementia onset (paper 3).
- Dementia-free participants showed increasing difference in cognitive scores over time according to activity levels, indicating physical activity to be increasingly important with ageing for cognitive health (paper 3).

5.2 Methodological considerations

5.2.1 Internal validity

Internal validity describes the inferences on the tested population from the tested variables. Violation of internal validity is usually classified into confounding, selection bias, and information bias (156).

Bias

Bias describes a systematic error when measuring, that happens at every registration systematically, and not by chance. All results will be skewed from the truth. When there is systematically error in measuring, it can show positive findings where there are none. This is called type 1 error. It can also measure no findings, when there should have been, called type 2 error (156).

All large health surveys must acknowledge possible, or even probable, selection bias. Populations with high morbidity, frailty, cognitive impairment, poor health, serious psychiatric illness, poor lifestyle, and low interest in health care are often underrepresented. This could result a discrepancy between the sample and the population they were meant to represent. However, the Tromsø Study has a high attendance rate, and includes a large number of participants, which strengthens the study. The dementia register is strengthened by having collected diagnoses from the only hospital in a large geographical area. Nonetheless, there is no register of those with dementia who have never visited the hospital, and occasionally dementia is not coded when admitted for other conditions. To minimize selection bias, we updated our register with death causes and included only six more who had died from dementia. The underreporting of dementia in death certificates raised concern, but the Swedish study SveDem (157) analysing 28 609 participants from primary and specialist care in the years 2007-2012, found that dementia diagnoses were missing from 37 % of death certificates (157). In Norway, a comparable large-scale registry is currently lacking. However, the Norwegian Cause of Death Registry observed a slight decrease in dementia related deaths in 2019 (158). This suggests that increased awareness among doctors may not be the sole factor contributing to the rise in dementia deaths over the past few decades. If increased awareness alone where the cause, the upward trend in the registry should persist. However, increased awareness is probably an factor, indicated by the increasing registration numbers in dementia as underlying or contributing cause of death has increased since 1972 (6.2%) to 2009 (50.2%) (159). The exact number of under-reporting dementia as death cause is not known, but if are comparable to SveDem (157), we have found 6/10 cases in death registries.

In paper 1 we used alcohol intake as a variable. This could introduce information bias, as people are prone to underreport alcohol use, especially young males and middle aged females (160). Alcohol use information could also be imprecise for a certain population due to selection bias, as shown by a study done in comparable area in Norway where both heavy drinkers (OR = 1.27) and abstainers (OR = 1.64) had higher risk of non-participation (161). Cognitive testing could also introduce a selection bias, as people with cognitive impairment tend to be more vulnerable, could have difficulties in responding to invitations, and with the execution of the survey itself. For this reason, non-responders could represent people with cognitive health problems.

The opposite must be considered with self-reported PA, which is often over-estimated by the subject. In the Tromsø Study, this has been thoroughly studied in a report comparing self-reported and objectively measured PA in Tromsø6 using an accelerometer (Actigraph LLC), with good correspondence (intraclass correlation = 0.63 for women and 0.59 for men) with reported and measured PA (143). However, they did report that in the group of men in the ages of 40-44 years, more reported vigorous PA if they also attended the activity study, suggesting physically active men are more likely to participate in health surveys addressing PA.

The Tromsø Study is a repeated cross-sectional cohort study. We considered test-retest reliability on cognitive tests. As 7 or 15 years passed between testing, we considered learning bias unlikely. Studies done in a geriatric population with a test comparable to Word Test 1 and Word Test 2 found increased reliability after one year (147).

In the establishment of the dementia registry, we observed a lower frequency of dementia diagnoses in departments other than geriatrics and old age psychiatric units. While we did not assess the severity of dementia at the time of diagnosis, it is plausible that departments lacking specialized competence in dementia diagnosis may have only identified severe cases or those already diagnosed by general practitioners.

5.2.2 External validity

External validity describes the generalizability of the study, how the results comply to the population who have not participated in the study (156). The Tromsø Study is comprised of a large, randomly selected cohort of community dwelling middle aged and older adults in the municipality of Tromsø (137, 139). Tromsø, located in the northern part of Norway, is a sizable

city with an approximate population of 77,000. Geographically expansive, it encompasses both central and rural areas. In Norway, central areas have a higher percentage of inhabitants with higher education and for North-Norway, central areas also have higher employment rate (162). Approximately 11% of households in Norway fall under the category of low-income, a figure that is relatively modest from an international perspective, but aligns with comparable rates in other Nordic countries (163). Norway boasts a robust healthcare system funded through taxation, adhering to principles of universal access. This structure contributes to increased longevity, with life expectancy reaching 83.3 years for women and 79.1 years for men between 2003 and 2017. This is an increasing trend over the last 100 years. In the same time period life expectancy in Tromsø was 83,9 for women and 79,6 for men, which is slightly higher than the national average (164). Longevity in Norway ranks between 11th to 17th highest internationally (165). As for cardiovascular risk factors the population of Tromsø is similar to the rest of Norway, and in line with large, European multicentre studies (166).

The first paper included only cognitively healthy participants over the age of 60. Given the Tromsø Study's random selection of participants, high participation percentage and number of subjects, the results from this paper have good external validity for this age group for a Western Caucasian population. Generalizability for those under 60 years old, is from this paper alone more uncertain. For paper 2 on dementia incidence, the large number of cases suggests identification of most dementia cases in the sample from the Tromsø Study, thus implying a good external validity for incidence of dementia in the general Norwegian population and similar Scandinavian populations of Caucasian origin. In paper 3 we analysed both cognition and dementia in participants above the age of 50 years, reproducing similar results to those from paper 1 with improved cognition in later born birth cohorts, as well as new results when comparing those later receiving a dementia diagnosis. Since we find similar trends in cognition when including a younger cohort, both paper 1 and paper 3 probably have good generalizability in similar populations above the age of 50.

The study's findings indicate that changes in risk factors over time have a significant impact on both cognition and dementia incidence. Considering external validity, the generalizability of these findings may be best applicable to populations with similar risk profiles such as in high-

income countries with predominantly Caucasian populations, and good access to education and healthcare services.

5.2.3 Missing data

In paper 1 all missing data on covariates was imputed. The analyses were done separately for each cognitive variable as a dependent variable. In paper 2, risk factors were not analysed, and thus, missing data was not an issue. For paper 3, missing values were excluded. For PA, 595 participants were missing. In addition, 875 participants had not reported PA at all visits. Only visits with missing PA information was then excluded.

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5.3 Discussion of main results

5.3.1 Trajectory of cognition in older adults

In paper 1 we found substantial improvement in later born birth cohorts. For Word Test 2, 80-year-olds tested as good as 60-year-olds tested 15-16 years prior. The finding of increased cognition is consistent with studies from other countries (29, 167, 168), and confirms that cognition is still rising in later born older adults compared to earlier born, measured at the same age.

A review from 2017 (167) studying the Flynn effect in those over 50 years old in 10 European countries, described a rise in cognition, but the gain was significantly smaller in countries already starting at a high scoring level. They were tested between 2004 and 2013, with participants of 50 to 84 years age. They used an immediate recall test, which is similar to Word Test 1 used in the Tromsø Study. The highest improvement of immediate recall measured as mean test score, was found in France (0.98), Italy (0.92), and Spain (0.84). Denmark (0.51), Sweden (0.46) and Germany (0.25) had the lowest improvement. Considering the geographical proximity, cultural similarities, and economic parallels between Norway and its neighbouring countries Denmark and Sweden, it is intriguing to observe a test score improvement of 0.87 (mean difference) in The Tromsø study. The superior test score in Tromsø could potentially be attributed to the temporal difference, as The Tromsø Study spanned a period 5 to 6 years longer, commencing 3 years prior to and concluding 2-3 years after the comparative studies in Denmark and Sweden. This observation suggests that the plateau for cognitive improvement in later-born birth cohorts among middle-aged and older adults in Norway has not yet been reached.

However, this plateau has been identified among the younger population, according to IQ-testing conducted on over 960,000 Norwegian military conscripts, predominantly men, spanning from the mid-1950s to 2002 (34). The first plateau, accompanied by a slight decrease, occurred in the period from 1978 to the early 1980s. Subsequently, IQ scores exhibited an upward trend until the mid-1990s, followed by a renewed decrease (34).

The explanation for this is probably multifactorial. Firstly, the military conscripts are tested at a younger age compared to the older participants in our study, despite being in overlapping birth cohorts. Consequently, being younger, they have been less exposed to risk factors for cognitive decline and have not benefited from the improvement of these risk factors within the population. Secondly, the flattening of the Flynn-effect, a phenomenon observed to have commenced in the latter decades of the last century (36), mainly corresponds to later born birth cohorts than the participants in our study. Additionally, the predominantly male composition of the young participants implies that improvements in educational levels among women will not be reflected in the results.

In paper 1 we found substantial sex differences in cognition. Women scored better than men in three of four cognitive tests, challenging short term verbal memory, long-term verbal memory, episodic memory, psychomotor ability, sustained attention, processing speed, episodic memory, and executive function. Women were, however, outperformed by men in the fourth cognitive test, challenging psychomotor speed (FTT). The same trend was seen in the review testing immediate recall in 10 countries, but it was not tested (167). However, this report stated that women started at a lower point, and improved more than men did. In our study this was not the case, as women both started and ended at a higher point in immediate recall. This was seen in both crude mean at T5 and T7, and in regression coefficients, implying that women also had a larger gain in short term memory than men did, from 2001 to 2015/2016.

In the FTT, men outperformed women, however, women had greater improvement in this test over time. Men did not have the higher improvement than women in tests where they were outperformed. If this trend is to continue, it is possible that women will outperform men in all these cognitive areas in the future.

The explanation for the sex-difference is probably multifactorial. Biological reasons would implicate a difference in function from a physiological or anatomical perspective between the

sexes. Several MRI studies have implicated a sex-difference in grey matter brain volume (169, 170), but how this directly relates to cognitive differences in different domains has not been thoroughly explored. Men's healthy brains where larger in the cerebella, hippocampi, thalami, caudate, and amygdala, while females had larger cingulate, precunei, frontal, and parietal cortex (170). This could imply that men and women have different areas of advantage, and that cognitive testing favours women's cognitive strengths.

A 2019 review of 40 countries found a female advantage in working memory, even more so for countries with higher levels of education (171). Education in paper 1 was the strongest mediator of cognitive improvement. Education is used to explain the Flynn Effect, and is suggested as protective for dementia (81). Education levels have changed drastically the latest decades in the Tromsø Study population, illustrated by the graph below showing education levels in 40-49-year-olds in different birth cohorts, stratified by sex.

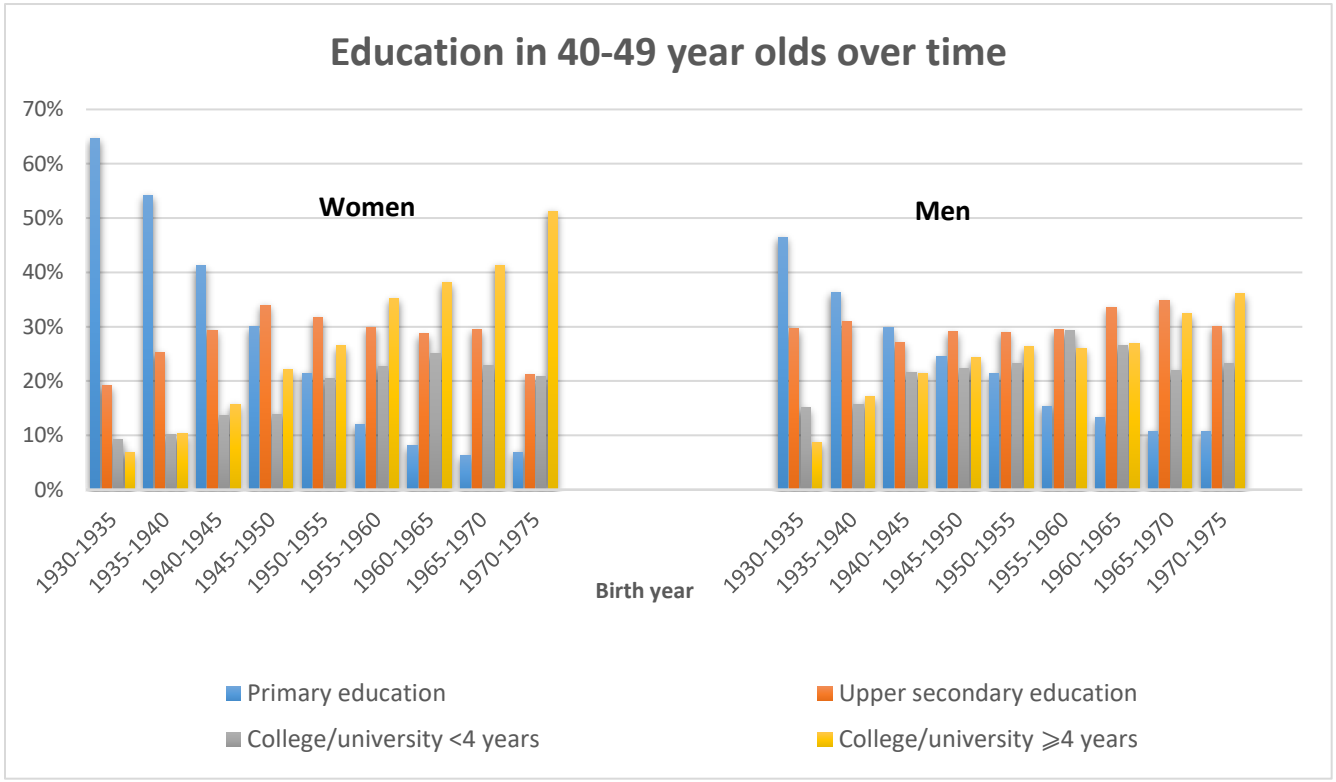

Figure 13: Graph over education levels for 40-49 years old and the sex-differences over time from birth-year 1930 to 1975. Graph is made by data from the Tromsø Study

As demonstrated in the graph above, education levels have increased in both sexes, but for women this trend is striking, surpassing men's education level for the latest birth cohorts. This could partly explain the sex difference seen in cognitive scores in the Tromsø Study.

Moreover, over the last century, there has been a notable shift in employment dynamics, characterized by an increasing participation of women in the workforce (172, 173). A recent study examining individuals aged 50-75 identified sex-based differences in late-life cognition linked to employment status during the ages of 20 to 50 and adherence to traditional gender roles (174). The study revealed that part-time employment conferred cognitive benefits for women but not for men. The authors posited that this effect could be attributed to women experiencing a positive impact from the integration of family responsibilities and career pursuits, providing cognitive stimulation—an aspect lacking for men. Notably, cognitive scores for women decreased similarly to the men's when they had extended periods out of work. Additionally, the study explored gender norms, revealing that adherence to traditional beliefs where men are expected to work and women to stay home, was associated with lower cognitive functioning in both sexes.

Another notable sex difference identified in paper 1 revealed a positive association between height and cognition. Women's height had not increased over the same time period, so the effect was only eminent in men. Height has been used as a proxy for nutrition and health care (33), so the effect is probably an enhanced cognition due to better health and nutrition. In another study looking at female nurses, they found an 8% decrease in the odds of healthy aging per standard deviation increase in height (175). Healthy aging included memory, but also chronic diseases, physical functioning, and mental health. This suggests several possibilities: that improved health and nutrition did not lead to a parallel increase height in women, that the observed effect in women is comparatively smaller, or that men had a greater potential for growth due to improved health care and nutrition in the first half of the last century. This pattern is further substantiated by a Danish study of over 700,000 military conscripts born between 1939 and 1959, showing that taller body composition at the entry of adulthood was associated with a lower risk of dementia diagnosis later in life (176).

In paper 1, an observed positive association was found between drinking frequency and cognition. Notably, the number of units consumed per occasion did not exhibit a significant

association with cognitive performance. Furthermore, the drinking pattern of middle-aged and older adults in Norway has changed over the last decades (177). In a study from 2010, wine consumption was identified as positively associated with better cognitive performance in both men and women, while abstaining from alcohol was associated with lower cognitive performance (178). Despite the suggestion of a U-shaped pattern for cognitive decline due to alcohol consumption (179, 180), research conducted on hippocampal atrophy indicates a dose-dependent decrease in volume with increasing units per week, even at moderate consumption (181). High socioeconomic status has been linked to heightened drinking frequency, but not with an increase in units consumed per occasion (182). Additionally, alcohol consumption correlates with increased social interactions (183), whereas social isolation demonstrates a negative association with cognition (81). These findings suggest that alcohol may not be the direct causal factor for the cognitive improvement shown with increased drinking frequency, but rather a proxy for factors such as high education, increased social interaction, and a higher socioeconomic status. Notably, our results indicating a positive association between cognition and alcohol remained robust even after adjusting for education.

Moreover, a notable sex-difference emerged in smoking habits, with smoking cessation exhibiting a positive association with cognition, with statistical significance in men. This discrepancy may be attributed to variations in smoking patterns between men and women, given that men were accountable for over 70% of all cigarettes smoked in Norway from 1927 to 2009 (184). Women initiated smoking later in the 20th century, and despite an increasing trend until around 1975, they did not reach parity with men until approximately 2000. Even as the overall prevalence of smoking is diminishing in both genders, men who smoke continue to consume a greater quantity of cigarettes than their female counterparts (184).

5.3.2 Dementia incidence

In Paper 2, our findings indicated a noteworthy decline in dementia incidence over the past two decades. The decline was evident in all age groups above 60 years old. Dementia cases diagnosed in individuals under the age of 65 are termed 'young onset dementia,' and individuals within this category are more predisposed to experiencing a steeper cognitive decline, particularly when the dementia is due to Alzheimer’s disease (185). Despite this, there is not a

substantial difference in life expectancy between young onset and late onset dementia (186). Additionally, early onset Alzheimer's disease tends to exhibit greater homogeneity, but higher levels of neuropathology compared to late onset Alzheimer's disease, which also shows more non-Alzheimer's neuropathology co-morbidity (187, 188). A study on early onset dementia (n=89) from Norway found incidence in 2015/2017 to be 25 per 100 000 person-year (189). Our study confirms these numbers, as the incidence rate in ages 50-59 on average was 26 per 100 000 person-years. We found no association with time, suggesting the incidence to be unchanged in this age group since year 2000. The largest decrease in incidence in our study was seen in the age group 60-69-year-old with a decrease of 61% from 2000 to 2019. Collected in 5-calendar-year groups the incidence decreased 2.7 to 1.1 per 1000 person-years. In the group of 70-79-year-old, incidence decreased from 15.2 per 1000-person years to 7.7 per person years.

To the best of our knowledge this is the first study of incidence of all-age dementia over time in Norway. Comparative analyses with international studies reveal a notable congruence, with similar incidence rates and an overall decline observed in Scandinavia, Europe, and the United States(85, 87, 190). Nevertheless, in England, a recent investigation reported a reversal in the incidence trend, with rates showing an upward trajectory since 2008 (191). England has witnessed changes in several concurrent conditions, including a plateau in mortality rates as well as an epidemic of obesity and type 2 diabetes, both of the latter recognized risk factors for dementia. Additionally, the study identified a swifter rise in dementia rates after 2008 among individuals with lower educational attainment.

The dementia registry was compiled from hospital diagnoses, supplemented by death cause registry data, without the inclusion of primary care or nursing home records. Acknowledging potential underrepresentation, a 2017 study conducted in nursing homes found that 55.9% of dementia diagnoses were absent from the records (192). They did not discuss the different record system between hospitals and primary care, but identified various factors contributing to this underreporting, such as the advanced stage of dementia in many admitted individuals rendering a diagnosis inconsequential, underdiagnosing by nursing home physicians, and discrepancies between researchers' dementia criteria and those employed by primary care physicians. It is important to note that this study was not specific to the Tromsø municipality, which boasts a unique setup—being home to the sole hospital within a 230 km radius. In Tromsø, individuals

with dementia are likely to receive the diagnosis at the hospital, where they undergo comprehensive assessments for various physical and psychiatric conditions. Additionally, it is noteworthy that Norway released its first national guidelines for diagnosing dementia in 2017 (193), emphasizing the role of general practitioners in the initial evaluation of dementia. Paradoxically, during the period covered by the dementia registry, nursing homes in Tromsø mandated a dementia diagnosis from a geriatric outpatient clinic for admission, a fact not explicitly documented, but verbally attested, by the former Chief Doctor of the Geriatric Department, Dr. Sigurd Sparr.

Risk factors have improved over the latest decades, and this has according to our research, improved cognition in the general population (paper 1). Therefore, it was of great interest to see that this improvement in brain health is also seen in the age-specific dementia incidence. A study from Norway in 2020 showed that prevalence of dementia is high (82), and that a large part is attributable to increasing life expectancy. In 2019 “Statistics Norway” forecasted that by 2030 the number of people above the age of 60 will for the first time in Norwegian history be higher than the number of people under the age of 20, and that by 2060 20% of all inhabitants in Norway will be over 70 years old (194). According to this forecast the number of people living with dementia will increase 2.3-fold over the next 30 years. This forecast has accounted for incidence to be stable. However, a study from the United States from 2022 showed a decrease in proportional prevalence as well as incidence, (195), even though the absolute numbers of dementia cases increased due to extended longevity. As our study finds decreasing incidence of dementia, future forecast of dementia cases in Norway might need adjustments.

As we have found the Flynn effect to be valid for those over 50 years old, we could also argue that the protective factors improving brain function, could contribute to continuous decreasing incidence of dementia in those over 60 years old.

We did not find a sex difference in incidence of dementia. Our observation differs from results found in the UK biobank study from 2021 (196), that found women had a lower risk of incidence dementia (HR 0.83). The participants were similar to ours in composition, but they had a larger number of participants, with 502 226 participants, and from these, 4068 dementia cases. As they had a higher number of participants, they might have discovered a sex-difference in incidence, that we did not with 10% of their population. Another study only found a sex difference with

higher risk of incidence dementia for women after the age of 80 years old (197). The Alzheimer Cohort Consortium (85) found similar incidence results as ours regarding similar incidence rates in men and women, in seven large cohorts (the Age, Gene/ Environment Susceptibility (AGES)–Reykjavik Study, the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), the Cognitive Function and Ageing Studies (CFAS), the Framingham Heart Study (FHS), the Gothenburg population studies, the Personnes Ag´ees QUID (PAQUID) study, the Rotterdam Study (RS), and the Three-City Study). The cohorts consist of a substantial number of individuals with similar compositions, potentially yielding comparable results. Nevertheless, a sex difference in cumulative 5-year hazard ratio was identified, with men exhibiting a more pronounced decrease in incidence ratio per decade compared to women (24% vs 8%) (85). It is pertinent to note, however, that the study included a higher proportion of women (59%) than men, and considering the shorter life expectancy of men (165), a potential survival bias may be present.

5.2.4 Cognition, dementia and physical activity

In paper 3 we examined PA in relation to cognition and dementia. What contrasts this study from many earlier studies on PA and dementia, is that we did not use PA to examine whether PA protects from incident dementia. Instead, we examined how PA-level was associated with cognition years before onset of dementia, when compared to PA's impact on cognition in dementia-free. We found PA to be positively associated with global cognition in those not developing dementia at a later point. For those developing dementia, PA was not associated with improved cognition earlier in life. As the evidence suggests, neurodegenerative pathology associated with Alzheimer's disease becomes apparent in the brain up to two decades before the onset of dementia (198). Similarly, other subtypes of dementia, including vascular disease (49, 52), Lewy body dementia, and frontotemporal dementia, have also shown evidence of neuropathology through dementia markers or radiological assessments. Our study found that both inactive and active participants in the dementia group scored lower on cognitive tests, compared to dementia-free at the same activity level, even before clinical disease onset. This suggests that PA improves cognition in healthy brains, but the effect on cognition when neurodegenerative disease is present, is questionable. However, we saw an effect of moderate

and very active PA on women later developing dementia, in the most sensitive cognitive test, Digit Symbol Coding. Only very active men demonstrated similar effect. As we already had unmasked sex differences in cognition in paper 1, this was very interesting. Word Test 1, testing short term memory, also had a significant positive association with PA in women in the dementia group, but this association disappeared when adjusted for education. The effect on Digit Symbol Coding, however, remained statistically significant after adjusting for education. This association suggests that PA has a greater effect on the female brain, than on the male brain, and that women's lesser education level in this birth cohort is not the only explanation, however probably a significant factor. Some studies investigate if this finding could be due to different effects on BDNF related to sex-hormones (199), with a female advantage of the neuro-proliferation. The effect on brains with neurodegenerative pathology seems to be much lower than in healthy brains, and to unmask the effect would need even more sensitive neuropsychological testing.

A comprehensive study published in Lancet in 2018 (200) identified a global tendency for women to engage in less leisure time PA than men. This observation aligns with precious findings from the Tromsø Study (201). The Lancet study postulates that women tend to do less leisure time PA, and lower-intensity activity than men do. Notably, for the participants in our study, who have witnessed evolving gender roles and increasing female enrolment in higher education over the last century in Tromsø, it is anticipated that the historical gap in PA levels between genders may narrow down in the future.

We found that in dementia-free participants, older adults who were physically active, had an increasingly gap in cognition with age, compared to the dementia-free inactive older adults. This result confirms those from a Whitehall study from 2017 (202), finding the difference in effect of PA on cognition to be four times higher in 80-year-olds than in 50-year-olds. This could suggest that PA has an increasing effect on cognition while aging. Conversely, it could also be a result of competitive risk from other diseases for those with poorer health.

Education is known to increase cognitive reserves (21). As expected, the Tromsø Study's participants with higher levels of education scored better on cognitive tests, than those with lower levels education did. What was of interest though, was that years before dementia onset, those with high education and probable preclinical dementia pathology, scored as low as those with low education who remained dementia-free. These results strengthen the cognitive reserve

theory (21), which postulates that those with a high cognitive reserve do not escape dementia, but debut later and with more severe symptoms. In statistical analysis this delay of onset clinical dementia, possibly shows as a preventive effect. This could explain some of the sex differences, as older women who are concurrently outliving men today have lower education level, thus lower cognitive reserves and are in greater risk to develop dementia.

6 Conclusions

Cognitive function is improving in dementia-free, community dwelling older adults. Later born birth cohorts are scoring significantly better than earlier born. Women outperform men in all tested cognitive domains, except psychomotor speed. Improvement of cognition over 14-15 years is more pronounced in women and does not seem to flatten out. This suggests that the Flynn effect is still valid in older adults, and there is still potential to improve cognition further. According to our analysis, higher education, PA, and maybe alcohol consumption, is key to keep improving cognition. For men, it is also of effect to stop smoking, and to have a good diet, the latter shown through increasing height.

We have observed that age specific dementia incidence is decreasing in ages 60-99 years old. There are no changes in incidence in the ages under 60 years, and no sex-differences overall in incidence over time.

PA does not improve cognition in people in the preclinical phase of dementia. It does, however, improve cognition in the dementia-free population, with increasing effect with age. Women seems to have a better effect of PA on cognition. People with high education, who later develop dementia, do as well on cognitive tests as dementia free with low education.

7 Clinical implications and future perspective

Cognition is still improving due to improvement of risk factors. With increasing life expectancy, this is promising for cognitive healthy aging, and could increase quality of life in old age. Improving brain health is also reflected in dementia incidence rates.

The Alzheimer Cohorts Consortium identified a general decline in incidence of 13% per decade across seven large studies conducted in Europe and the United States. Their projections suggest that this decline could potentially result in 15 million fewer cases by 2040, compared to the

initial estimates provided by the Global Burden of Disease (85). How this number will translate to Norwegian numbers is not studied in this thesis but will be of great interest to recalculate future prevalence in Norway, with our evidence of decreasing incidence. By directly calculating this numbers by using the estimates done by Gjøra et al in 2020 (82), and the decrease calculated by the Alzheimer Cohorts Consortium, we can estimate that future prevalence of dementia will go down from 192,789 to 167,726 cases in 2040, suggesting a reduction of more than 25 000 cases, which is a substantial burden release.

Our study did not find substantive evidence supporting a significant improvement in cognitive test scores among participants who later received a dementia diagnosis. This could be attributed to the progression of dementia pathology during the tested period, occurring prior to the onset of dementia, although this hypothesis was not explicitly examined. It is plausible that more sensitive tests could have detected changes that were not identified in our study. Nevertheless, given the well-established positive impact of physical activity on brain health, there might be an effect not captured in our analysis. Notably, we observed a robust and positive association between high levels of physical activity and cognition in participants who remained dementia-free. Considering that there is no routine screening for dementia pathology in cognitively healthy individuals, health authorities should emphasize the promotion of physical activity, healthy lifestyle, and higher education to enhance cognitive health in adults. The most significant effect was observed in the comparison between inactive and active individuals, with marginal changes noted between active and very active participants. Consequently, future recommendations should target sedentary adults and the elderly, encouraging them to engage in at least light activities such as daily walking, biking, skiing, and other low-intensity exercises. While those who are moderately active may have the potential to enhance their cognition further, the primary public health benefit lies in encouraging sedentary individuals to adopt physical activity.

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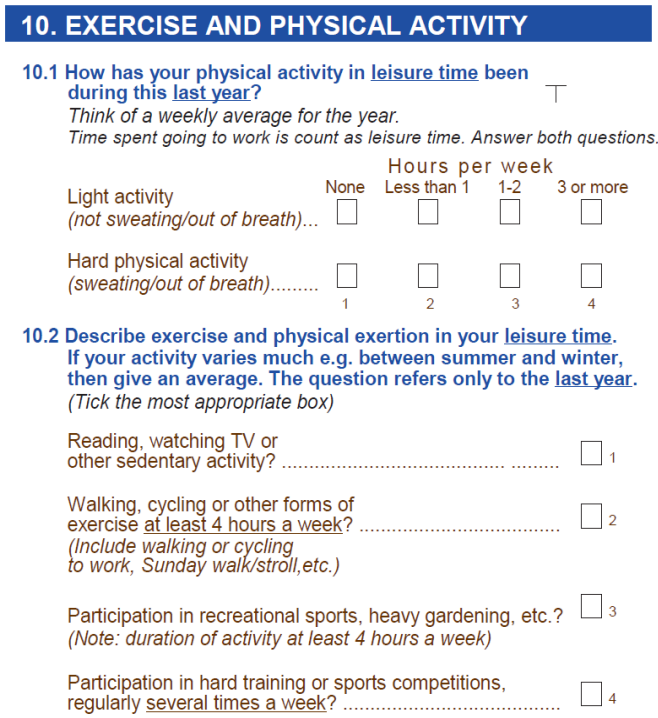
Appendix

Hopkin Symptom Check list-25 questions and scoring.

Coding of PA

Table e-1: Coding of the PA variable



10. EXERCISE AND PHYSICAL ACTIVITY

10.1 How has your physical activity in leisure time been during this last year?

Think of a weekly average for the year.
Time spent going to work is count as leisure time. Answer both questions.

	Hours per week			
	None	Less than 1	1-2	3 or more
Light activity *(not sweating/out of breath)...*	☐	☐	☐	☐
Hard physical activity *(sweating/out of breath).....*	☐ 1	☐ 2	☐ 3	☐ 4

10.2 Describe exercise and physical exertion in your leisure time. If your activity varies much e.g. between summer and winter, then give an average. The question refers only to the last year.

(Tick the most appropriate box)

Reading, watching TV or other sedentary activity? ..... ☐ 1

Walking, cycling or other forms of exercise at least 4 hours a week? ..... ☐ 2
(Include walking or cycling to work, Sunday walk/stroll,etc.)

Participation in recreational sports, heavy gardening, etc.? ☐ 3
(Note: duration of activity at least 4 hours a week)

Participation in hard training or sports competitions, regularly several times a week? ..... ☐ 4

PA	
10.1 Light activity	
1	0
2	0
3	0
4	0
10.1 Hard activity	
1	0
2	1
3	1
4	2
10.2 SGPALS	
1	0
2	1
3	2
4	2

Table e-1: To the left the two questions asked for physical activity. 10.1 is asked alone in Tromsø 4 and in Tromsø 5 for those over the age of 70, and 10.2 is asked in the remainder. 10.2 is Saltin-Grimby Physical Activity Level Scale described earlier.

Table e-2: Hopkins checklist

3.1 Below is a list of various problems. Have you experienced any of this during the last week (including today)?

(Tick once for each complaint)

	No complaint	Little complaint	Pretty much	Very much
Sudden fear without reason	☐	☐	☐	☐
Felt afraid or anxious	☐	☐	☐	☐
Faintness or dizziness	☐	☐	☐	☐
Felt tense or upset	☐	☐	☐	☐
Tend to blame yourself	☐	☐	☐	☐
Sleeping problems	☐	☐	☐	☐
Depressed, sad	☐	☐	☐	☐
Feeling of being useless, worthless	☐	☐	☐	☐
Feeling that everything is a struggle	☐	☐	☐	☐
Feeling of hopelessness with regard to the future	☐	☐	☐	☐
	1	2	3	4

RESEARCH OPEN ACCESS

Improved Cognitive Function in the Tromsø Study in Norway From 2001 to 2016

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Neurology: Clinical Practice December 2021 vol. 11 no. 6 e856-e866 doi:10.1212/CPJ.0000000000001115

Abstract

Background and Objectives

Physical capacity and cardiovascular risk profiles seem to be improving in the population. Cognition has been improving due to a birth cohort effect, but evidence is conflicting on whether this improvement remains in the latest decades and what is causing the changes in our population older than 60 years. We aimed to investigate birth cohort differences in cognition.

Methods

The study comprised 9,514 participants from the Tromsø Study, an ongoing longitudinal cohort study. Participants were aged 60–87 years, born between 1914 and 1956. They did 4 cognitive tests in 3 waves during 2001–2016. Linear regression was applied and adjusted for age, education, blood pressure, smoking, hypercholesterolemia, stroke, heart attack, depression, diabetes, physical activity, alcohol use, BMI, and height.

Results

Cognitive test scores were better in later-born birth cohorts for all age groups, and in both sexes, compared with earlier-born cohorts. Increased education, physical activity, alcohol intake, decreasing smoking prevalence, and increasing height were associated with one-third of this improvement across birth cohorts in women and one-half of the improvement in men.

Discussion

Cognitive results were better in more recent-born birth cohorts compared with earlier born, assessed at the same age. The improvement was present in all cognitive domains, suggesting an overall improvement in cognitive performance. The 80-year-olds assessed in 2015–2016 performed like 60-year-olds assessed in 2001. The improved scores were associated with increased education level, increase in modest drinking frequency, increased physical activity, and, for men, smoking cessation and increased height.

The Western population is getting older, and in Norway, the population older than 70 years is estimated to increase from 12% today to 21% in 2060.[1] It is well documented that aging is the largest risk factor for cognitive decline. Cognitive function has improved over the last century in the general adult population, a trend known as the Flynn effect.[2] However, a negative Flynn effect has been reported in the latest decades of the twentieth century,[3] suggesting that a plateau for the improvement

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

has been reached. The improvement in cognition is probably a cohort effect, commenced by multifactorial change in the population on factors influencing the brain and its function.[4]

Modifiable risk factors for cognitive decline have been identified.[5-9] Among these factors, education seems to be the most promising protecting factor for cognitive decline.[4,5] The population-based Tromsø Study in Norway has gathered a broad range of multidisciplinary health information from the adult population of Tromsø for five decades. The study has found improvement in cardiovascular risk factor profiles[10,11] and biomarkers of aging such as physical capasity measured by grip strength.[12] Therefore, we aimed to determine whether cognition has improved in later-born cohorts of older adults assessed 15 years apart. If so, which factors have contributed the most to this improvement?

Table 1 Birth Cohorts and Age Bands by Tromsø Study Wave

	Tromsø 5, year 2001	Tromsø 6, year 2007/8	Tromsø 7, year 2015/16
Birth cohort	Age, y (n total)	Age, y (n total/ n new)	Age, y (n total/ n new)
1914–1920	81–87 (115)		
1921–1927	74–80 (1,076)	81–87 (307/38)	
1928–1934	67–73 (1,506)	74–80 (806/90)	81–87 (247/14)
1935–1941	60–66 (1,600)	67–73 (1,230/202)	74–80 (959/134)
1942–1948		60–66 (1,788/1,788)	67–73 (1,995/804)
1949–1955			60–66 (2,157/2,157)
Total	4,297	4,131	5,358

Methods

The Tromsø Study is the longest-running Norwegian ongoing population-based longitudinal cohort study, with repeated screening of inhabitants in the municipality Tromsø, Norway.[13] Seven surveys (Tromsø 1–7) have been conducted since 1974. Participants were recruited based on the national registry data of adult inhabitants. Each survey included both new individuals and individuals who had participated before, based on a complex sampling design described elsewhere.[13,14] Cognitive testing was introduced in Tromsø 5 and repeated in Tromsø 6 and Tromsø 7.[13-15] The present study includes Tromsø 5–7 (Table 1 and Figure 1). Participants who had taken part in the second part of Tromsø 4 in 1994/95 and a random sample of participants attending for the first time[14] were eligible for invitations to the second visit in Tromsø 5–7. For the second visit in Tromsø 5, 85% of those eligible attended (n = 5,939), in Tromsø 6, 64% (n = 7,350), and in Tromsø 7, 60% (n = 7,804).[16] Participants aged 60–88 years who had completed at least 1 cognitive test (n = 9,514, 54.4% women) in Tromsø 5–7 were eligible for the present study. Of these, 6,034 had participated once, 2,708 twice, and 782 in all 3 surveys with 7 or 14–15 years apart. Those attending only Tromsø 5 had a higher mean age (Tromsø 5: 71.8 years; Tromsø 6: 65.9 years; and Tromsø 7: 65.2 years) and a higher percentage of participants with only primary education (85.7%) compared with those who participated only in Tromsø 7 (30.1%) and those participating in all 3 surveys (66%). Those only attending Tromsø 5 also reported less physical activity. They had a higher frequency of smokers, people with high blood pressure and hypercholesterolemia, but not more depression. (Table 2 and eTable 1, links.lww.com/CPJ/A301).

Participants were stratified in 7-year birth cohorts and 7-year age bands to prevent overlapping birth cohorts, as Tromsø 5–7 were performed 7 years apart. The age-specific analyses were performed in 4 age bands: 60–66, 67–73, 74–80, and 80–87 years.

The Mini-Mental State Examination (MMSE) was excluded from the analyses as it was first introduced in 2008, and we aimed to explore trends since 2001. We, however, did 2 MMSE sensitivity tests: first excluding participants with MMSE scores of 19 or lower (n = 10 in Tromsø 6 and n = 34 in Tromsø 7) and second excluding participants with MMSE 20–24 (n = 141 in Tromsø 6, n = 397 in Tromsø 7), to check for impact of participants with probable neurodegenerative disease.

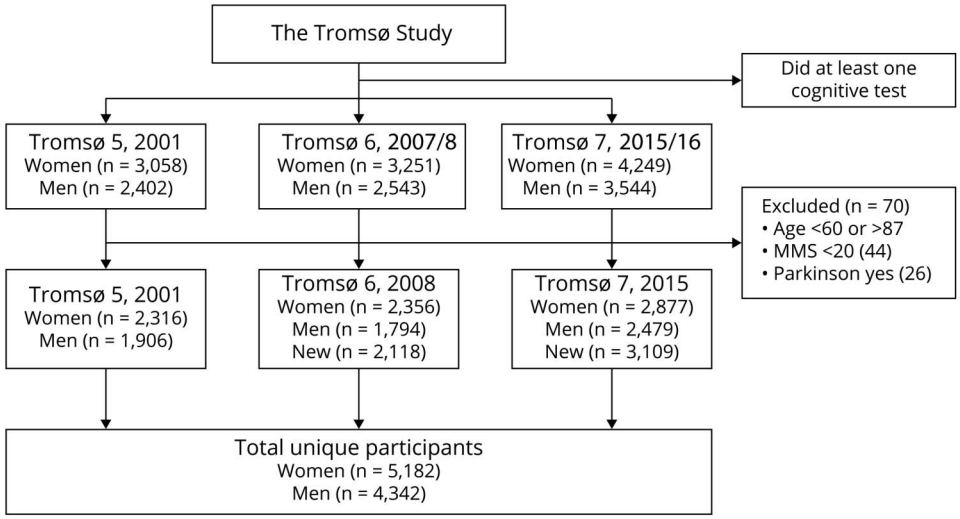
Measurements of Cognitive Function

Word test 1 (WT1) is a 12-word memory test of short-term verbal memory.[6] The participants were given 2 minutes to complete a free immediate recall of 12 nouns that were shown written on a board and read aloud at 5-second intervals. One point was given for correct recall of each word. Scores ranged from 0 to 12.[17,18] Word test 2 (WT2) is a test of long-term verbal memory, episodic memory, and the ability to use learning strategies.[6] The 12 words from WT1 were shown and read aloud again mixed with 12 new nouns. The participants were asked to identify each word as new or known. One point was given for each correctly identified word. Points ranged from 0 to 24.[17,18] The digit symbol coding test (DSCT) is part of the Wechsler Adult Intelligence Scale.[19] It is used to examine perceptual processing, perceptual motor speed, and memory[20] and is sensitive enough to reveal small changes in cognition, as it is influenced by psychomotor ability, sustained attention, processing speed, episodic memory, and executive function.[9] This test pairs 9 numbers with 9 symbols. Participants were asked to fill in as many correct symbols in numbered blank squares as they could in 90 seconds without skipping a square. The number of correct symbols was the score of the test.[6,21] In the finger-tapping test (FTT), a test measuring psychomotor speed,[22] the participants tapped their nondominant index finger on a button for four 10-second rounds. The result was the mean tapping count of the last 3 rounds.

Risk Factors for Cognitive Decline, Possibly Affecting Cohort Differences

We chose factors that are proposed as detrimental or beneficial for cognitive function: education, high blood pressure, smoking hypercholesterolemia, stroke, alcohol consumption, diabetes, depression, heart attack, physical activity, height, and body mass

Figure 1 Selection of Participants From the Tromsø Study



index (BMI).[5,6,23-25] Height is an indicator of nutrition early in life and health care.[26] Participants filled out questionnaires on life style. For details, see eAppendix 1 (links.lww.com/CPJ/A301).

Statistical Analyses

Data from all study waves were pooled and analyzed as 1 set. First, to investigate whether cognitive test scores improved in later-birth cohorts, we performed a multiple linear regression analysis in each of the age bands, with the respective cognitive tests as the dependent variable and study wave as the independent covariate. All models were adjusted by age and sex. Second, to investigate how much other covariates mediated the changes in test scores between study waves, covariates were added one by one in the whole age span (in the following order: age, education, blood pressure, hypercholesterolemia, smoking, stroke, previous heart attack, depression, diabetes, physical activity, alcohol units, alcohol frequency, height, and BMI), and we investigated the change in percent in the coefficient for the study wave. The interaction terms age × study waves and study wave × sex and sex × age and sex × age × study wave were included to allow for different changes over time by sex and age. We used Stata 14.2. There were 2,852 missing values in one or more of the covariates, which were adjusted with multiple imputation by chained equation. The imputation was based on the variables age, sex, and study wave and the respective cognitive variable. The cognitive test scores were not imputed. All missing values of the mediators were below 3.5%, except for alcohol consumption (n = 2,707), depression (n = 1,099), and physical activity. Physical activity in Tromsø 5 had a high missing rate (n = 2,852), as the participants older than 70 years (n = 1,615) were asked a different question.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was funded by Northern Norway Regional Health Authority (Helse Nord RHF). The Regional Committee for Medical and Health Research Ethics approved the study (REK Nord, reference 2016/389). Written informed consent was given by all participants.

Data Availability

Data cannot be made public as legal restrictions are set by the Tromsø Study Data and Publication Committee. Researchers can apply for data access at uit.no/research/tromsostudy/project?pid=709148.

Results

The mean age of the participants was 68.8 years, with the range 60–87 years and interquartile range 63–73. Description of participants can be found in Table 2. Education levels in the Tromsø municipality have increased markedly over the last century (eFigure 1, links.lww.com/CPJ/A301). We found an increase over time in people drinking alcohol 2 or more times per week, but they did not increase the amount of alcohol per occasion. Later-born participants reported more leisure exercise and smoking prevalence declined over time, especially in men. Rates of hypercholesterolemia decreased, and participants had better controlled blood pressure. There was a minor increase in BMI and diabetes, but little change in number of other comorbid conditions.

Scores in all 4 cognitive tests improved in later-born birth cohorts for all age bands, in both sexes by 5%–51% compared with earlier born tested at the same age (Table 3). The greatest improvement was seen in DSCT and the least in WT2.

Women scored better on short-term memory, long-term verbal and episodic memory, visuospatial function, perceptual motor speed, and sustained attention (WT1, WT2, and DSCT)

Table 2 Description of the Participants by Sex, Age, Survey, and Birth Cohort

Age	60–66				67–73				74–80				81–87			
Survey year	2001	2007/8	2015/16		2001	2007/8	2015/16		2001	2007/8	2015/16		2001	2007/8	2015/16	
Birth cohort	1935–1941	1942–1948	1949–1955	*p* Value	1928–1934	1935–1941	1942–1948	*p* Value	1921–1927	1928–1934	1935–1941	*p* Value	1914–1920	1921–1927	1928–1934	*p* Value
Women																
n	897	1,138	1,123		774	638	1,064		617	395	485		65	131	114	
Mean height, cm	168	163	164	<0.001	166	161	162	<0.001	165	160	160	<0.001	163	158	158	0.06
Low education, %	82	66	29	<0.001	85	78	45	<0.001	92	85	55	<0.001	89	88	63	<0.001
Smoking, yes %	28	20	16	<0.001	24	17	11	<0.001	16	15	8	<0.001	11	6	7	0.323
Inactive, %	15	19	11	<0.001	14	18	13	<0.001	NA	28	17	<0.001	NA	40	20	0.001
Alcohol, %				<0.001				<0.001				<0.001				<0.001
Teetotaler	12	13	7		17	22	12		26	31	23		21	50	29	
Monthly or less	50	30	23		57	36	28		55	38	34		62	30	37	
2–4 times/month	28	33	37		18	25	33		12	22	25		10	13	22	
2–3 times/week	8	17	27		7	13	20		5	8	11		7	4	9	
4≤ times/week	2	7	6		1	4	8		2	2	7		0	4	4	
5≤ units/occasion	0.7	1.0	1.1	0.538	0.5	0.6	0.5	0.948	0.5	0.2	0.2	0.640	0	0.5	0.8	0.788
7≤ units/occasion	0.1	0.2	0	0.348	0.5	0	0	0.01	0.2	0	0.2	0.680	0	0.5	0	0.581
Hypertension, %	48	44	30	<0.001	62	60	45	<0.001	68	68	59	0.002	77	75	71	0.576
High cholesterol, %	92	84	82	<0.001	91	81	77	<0.001	93	79	74	<0.001	94	79	70	<0.001
Depression, %	3.6	3.5	3.6	0.990	2.4	2.3	2.3	0.978	1.8	2.6	1.3	0.369	4.6	4.4	1.5	0.332
Heart attack, %	2.2	2.1	1.8	0.771	5.5	6.2	2.0	<0.001	8.1	8.4	5.1	0.088	17.2	9.9	4.5	0.014
Diabetes, %	4.0	4.2	5.5	0.186	4.6	8.9	7.9	0.003	7.2	7.0	9.1	0.409	6.3	10.9	9.5	0.663
BMI mean	26.9	27.4	26.7	0.003	26.9	26.9	27.7	<0.001	27.2	27.1	26.9	0.556	26.8	27.2	26.8	0.678
Men																
n	697	801	1,010		718	539	881		453	325	405		50	92	106	
Mean height, cm	168	177	177	<0.001	167	175	176	<0.001	166	173	174	<0.001	165	172	173	<0.001
Low education, %	71	53	24	<0.001	78	65	32	<0.001	82	70	36	<0.001	80	79	42	<0.001

Continued

Table 2 Description of the Participants by Sex, Age, Survey, and Birth Cohort *(continued)*

Age	60–66				67–73				74–80				81–87			
Survey year	2001	2007/8	2015/16		2001	2007/8	2015/16		2001	2007/8	2015/16		2001	2007/8	2015/16	
Birth cohort	1935–1941	1942–1948	1949–1955	*p* Value	1928–1934	1935–1941	1942–1948	*p* Value	1921–1927	1928–1934	1935–1941	*p* Value	1914–1920	1921–1927	1928–1934	*p* Value
Smoking, yes %	27	17	14	<0.001	26	16	11	<0.001	17	14	7	<0.001	6	8	7	0.02
Inactive, %	17	17	12	<0.001	14	15	15	<0.001	NA	21	15	0.017	NA	22	17	0.123
Alcohol, %				<0.001				<0.001				<0.001				<0.001
Teetotaler	3	4	5		5	11	5		6	15	11		6	30	14	
Monthly or less	40	26	17		50	32	21		58	34	30		67	38	38	
2–4 times/month	36	39	37		29	33	39		20	33	32		17	16	27	
2–3 times/week	16	23	32		11	17	24		10	15	18		4	6	15	
4≤ times/week	4	8	9		4	8	11		5	3	9		6	9	6	
5≤ units/occasion	7.9	7.5	9.4	0.306	3.9	3.8	3.9	0.995	2.6	2.6	1.8	0.665	0	0.8	1.8	0.561
7≤ units/occasion	1.2	1.6	2	0.419	1.0	0.2	0.6	0.206	0.4	0.8	0	0.193	0	0	0	
Hypertension, %	53	52	35	<0.001	55	54	42	<0.001	66	62	49	<0.001	60	63	54	0.332
High cholesterol, %	85	73	64	<0.001	80	65	57	<0.001	80	59	47	<0.001	84	53	42	<0.001
Depression, %	1.2	0.8	1.9	0.132	1.5	1.9	0.4	0.025	2.4	2.7	0.4	0.031	2.0	0.8	1.8	0.758
Heart attack, %	11.6	7.2	6.7	0.001	15.0	15.2	9.9	0.002	19.2	22.4	11.7	<0.001	20.8	21.9	13.2	0.198
Diabetes, %	5.4	6.9	7.1	0.324	5.3	8.9	9.9	0.003	6.0	7.7	11.9	0.003	10.6	8.3	6.7	0.702
BMI mean	27.0	27.7	27.8	<0.001	26.4	27.2	27.9	<0.001	26.3	26.7	27.4	<0.001	25.0	26.6	26.9	0.005

Abbreviation: BMI = body mass index.
Low education: primary up to 10 years; inactive: low physical activity on leisure time; hypertension: systolic blood pressure >140 and/or diastolic blood pressure >90; cholesterol ≥5 mmol/L; depression is reported for last week.
p Values obtained by χ-square test for categorical variables and 1-way analysis of variance for continuous variables.

Table 3 Cognitive Crude Mean Scores at Tromsø 5 and Tromsø 7 and Difference in Regression Coefficient in Adjusted Models

			Difference in cognition					
			Model 1			Model 2		
Age	Mean crude test score at T5	Mean crude test score at T7	Change in cognition regression βT5–βT7	95% CI marked with *p* value	% Change cognition regression βT5–βT7	Change in cognition regression βT5–βT7	95% CI marked with *p* value	% Change cognition regression βT5–βT7
Word test 1, number immediately recalled 0–12								
Women								
60–66	6.70	7.64	0.9	0.8 to 1.1***	16.1	0.5	0.3 to 0.7***	7.9
67–73	6.06	7.04	1.0	0.8 to 1.1***	17.5	0.5	0.4 to 0.7***	9.9
74–80	5.47	6.37	0.9	0.7 to 1.1***	18.0	0.6	0.3 to 0.8***	10.6
81–87	4.85	5.38	1.1	0.6 to 1.7***	25.1	1.0	0.4 to 1.5**	17.5
Men								
60–66	6.38	7.19	0.8	0.6 to 0 0.9***	13.4	0.3	0.1 to 0.5**	6
67–73	5.66	6.51	0.8	0.7 to 1.0***	17.6	0.4	0.2 to 0.6***	10.9
74–80	5.18	5.96	0.8	0.5 to 1.0***	17.1	0.3	0.0 to 0.6**	9.1
81–87	4.73	5.59	0.9	0.3 to 1.5**	19.5	0.5	−0.2 to 1.2	6.6
Word test 2, recognition of words 0–24								
Women								
60–66	21.45	22.48	1.0	0.8 to 1.2***	9.9	0.7	0.5 to 0.9***	3.6
67–73	20.75	22.21	1.4	1.2 to 1.7***	7.6	1.1	0.9 to 1.3***	5.9
74–80	20.40	21.62	1.2	0.9 to 1.5***	6.6	0.9	0.5 to 1.2***	4.4
81–87	20.09	21.47	1.6	0.7 to 2.6**	9.8	1.6	0.6 to 2.6**	8.2
Men								
60–66	21.18	22.19	1.0	0.8 to 1.2***	5	0.6	0.4 to 0.9***	3.5
67–73	20.62	21.88	1.3	1.0 to 1.5***	6.7	0.9	0.7 to 1.2***	5.2
74–80	20.35	21.29	0.9	0.6 to 1.3***	5.2	0.7	0.3 to 1.1***	4
81–87	20.45	21.46	1.0	0.1 to 1.9*	5.2	0.3	−0.7 to 1.3	2.6
Digit symbol coding, sum correct symbols in 90 s								
Women								
60–66	34.84	45.54	10.5	9.5 to 11.4***	33.3	7.2	6.2 to 8.1***	22.5
67–73	28.77	39.92	11.0	10.0 to 12.0***	42.9	7.8	6.8 to 8.6***	30.7
74–80	24.54	33.08	8.6	7.4 to 9.6***	38.8	5.8	4.6 to 7.0***	26.4
81–87	20.21	26.86	7.3	4.0 to 10.6***	41.1	6.1	2.9 to 9.3***	31
Men								
60–66	33.7	41.09	6.9	5.8 to 7.9***	22.7	3.8	2.5 to 4.6***	12.7
67–73	27.38	36.81	9.3	8.3 to 10.2***	38.2	6.0	5.0 to 7.0***	25.1
74–80	23.51	30.90	7.3	5.9 to 8.8***	37.8	4.2	2.7 to 5.7***	22.3

Continued

Table 3 Cognitive Crude Mean Scores at Tromsø 5 and Tromsø 7 and Difference in Regression Coefficient in Adjusted Models *(continued)*

			Difference in cognition					
			Model 1			Model 2		
Age	Mean crude test score at T5	Mean crude test score at T7	Change in cognition regression βT5–βT7	95% CI marked with *p* value	% Change cognition regression βT5–βT7	Change in cognition regression βT5–βT7	95% CI marked with *p* value	% Change cognition regression βT5–βT7
81–87	22.5	25.94	3.9	0.5 to 7.3*	17	1.3	−1.9 to 4.5	4.7
Finger tapping test, sum tapped nondominant finger 10 s								
Women								
60–66	48.59	52.17	3.4	2.7 to 4.2***	8.5	2.0	1.2 to 2.8***	5
67–73	45.32	48.30	2.9	2.1 to 3.7***	8.6	1.3	0.4 to 2.2**	4.5
74–80	41.26	46.56	5.3	4.1 to 6.5***	15.9	3.7	2.4 to 5.0***	10.7
81–87	38.57	44.12	6.5	3.1 to 9.9***	26.3	5.2	1.6 to 8.8**	20.4
Men								
60–66	53.68	57.01	3.1	2.2 to 3.9***	7.5	1.3	0.3 to 2.2**	4.6
67–73	49.95	52.75	2.7	1.8 to 3.5***	7.6	1.3	0.3 to 2.2**	4.4
74–80	45.81	49.71	3.9	2.5 to 5.2***	11.1	2.5	1.1 to 4.0**	7.8
81–87	45.89	47.85	1.6	−2.0 to 5.1	4.2	−0.9	−4.6 to 2.9	−2.3

Age- and sex-specific multiple linear regression model, testing the change in cognitive score for each age group. Age groups are nonoverlapping. This means that participants are never in the same age group twice. Model 1: adjusted for age. Tromsø 5 and Tromsø 7 are used as independent variables. Model 2: model 1 + education, blood pressure, hypercholesterolemia, smoking, previous stroke, previous heart attack, diabetes, depression, activity, alcohol consumption, height, and body mass index. Change in β-Tromsø 7 is reported, and percentage change for the β-coefficient adjusted for both models. Mean values are crude means in age group for given survey. Percentage change is calculated by the regression coefficient of the logarithmic values for the cognitive test in given age group and sex, adjusted for model 1 and model 2. *p* Values are marked as follows: **p* < 0.05,***p* < 0.01, ****p* < 0.001.

compared with men (Table 3 and Figure 2). They also had higher age-specific improvement than men did over time (interaction for sex by study wave: $p < 0.05$ for all 3 cognitive tests). For psychomotor speed (FTT), however, the sex difference was reversed, with higher scores and larger improvement over time for men than for women. In DSCT, men improved more than women at older age ($\Delta\beta = 0.1$), and the opposite for the FTT, on which women improved more at older age ($\Delta\beta = 0.02$). On the FTT, older women had larger improvement over time in cognitive test scores than the younger women ($p = 0.008$), whereas for DSCT, younger women improved the most.

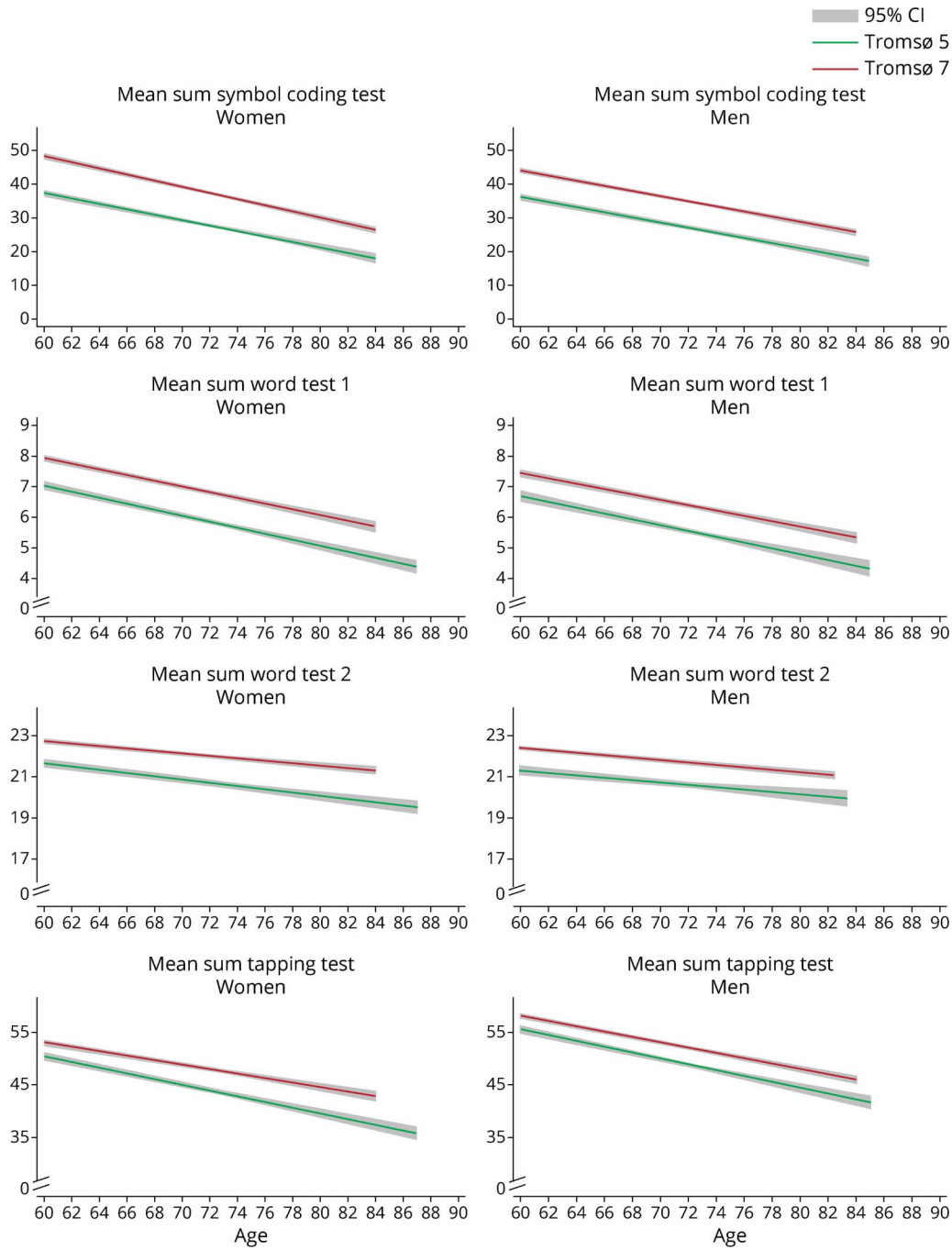
When adjusted for all included mediators, the cognitive test score improvements in later-born were still statistically significant, except in the oldest men (Table 3), indicating other factors mediating the improvement in the younger age bands. The most prominent mediator for improved cognitive scores in later-born birth cohorts was education. When the early-born and most recent born birth cohorts were compared, education mediated 40.6% of the improvement in female WT1 scores and 52.9% in male scores. It was less, but still a substantial mediator for the improvement on WT2, mediating more than 20% for both sexes. Education was mediating 19.9% in women and 31.3% in men, of the improvement on the DSCT results, whereas the results of FTT scores improved by 29.4% and 35.3% in women and men, respectively.

Increase in alcohol drinking frequency mediated 24.9% of the improvement in FTT score in women and 17.6% in men. For WT1, it mediated 23% of the improvement in women and 19.5% in men. Within each occasion, the effect of increasing consumption had a weak (0.6% or less) negative trend on all cognitive tests, equal for both sexes. Reporting more than 5 units of alcohol per occasion, was for men associated with decreasing test performance on DSCT and FTT. (men $p < 0.01$, women $p > 0.05$).

Increased physical activity was associated with improved test scores, especially in short-term memory and psychomotor speed, with a mediating effect of 4.2%–6.8% on cognitive outcomes.

Among men, less smoking in later-born birth cohorts mediated 12.2% of the improvement in the FTT and 9.3% of improvement in WT1, whereas in women, smoking was not a mediator. Increased height in later-born cohorts was associated with 21.3% of the improvement in WT1 in men and 7.6% in women. Conjointly, increased education, physical activity, alcohol intake, height and decreased smoking

Figure 2 Differences of Cognitive Scores With 14/15 Years Apart



Estimation is done with linear regression with 95% confidence interval (CI). The y-axis has scale brake for WT1, WT2 and FTT to better illustrate the age-specific improvement over time.

prevalence in later-born birth cohorts, mediated on average 34.4% (range 24.5%–47.7%) of the improvement in women's results on the 4 cognitive tests. Men's average improvement in the 4 cognitive tests on the same conjoined factors was 51.6% (range 35.8–73.4%).

We performed sensitivity tests excluding those having had a stroke, with no substantial difference in the results. We also excluded participants with Parkinson disease and all those with MMSE scores of 19 or below with no substantial difference in results. Excluding those with MMSE <25 from Tromsø 6 and Tromsø 7, enlarged improvement in cognitive scores as MMSE was not performed in Tromsø 5 (n = 581), the reference group. However, after removing those testing in the lower areas on MMSE in T6 and T7, the covariates had less influence on the change, with largest effect on short time memory (eTables 2–4 links.lww.com/CPJ/A301).

Discussion

In this large population-based study, we found improvement in cognitive test scores in more recently born birth cohorts. The scale of these differences varied in the 4 cognitive tests, but on the DSCT, the improvement corresponded to 12 years for women and 10 years for men, meaning that 70- to 72-year-olds in 2015/16 performed as 60-year-olds did in 2001. For WT1, the improvement was 10 years for both sexes, and for WT2, the test score improvement in was corresponding 20 years for both sexes, meaning that for recognition, 80 is the new 60 (Figure 2).

These positive associations were evident in all age bands and in both sexes represented in all 4 cognitive tests, covering different areas of cognition. The strongest mediating factors associated with improved cognition in more recent born birth cohorts were higher education levels, increased height, and smoking cessation for men and increased physical activity for both sexes. Higher cognitive test scores in those reporting more frequent, but yet moderate alcohol consumption was also observed.

Education was the most prominent mediator in the short-term memory test (WT1), suggesting that education may benefit short-term memory. Our results confirm the findings of similar studies in other Western countries where educational levels have improved in the last century.[27-31] Also in this study's population, education levels have changed immensely over the last century in both sexes (Table 2 and eFigure 1, links.lww.com/CPJ/A301). This indicates that education improves not only resilience to damage and cognitive reserve capacity but also cognition in those without manifest neurodegenerative disease.

Psychomotor speed also improved over birth cohorts. This supports the possible relationship between the improvement in cognition and the improved physical strength shown in earlier studies[12] and the weak association between cardiovascular risk factors and cognition.[27]

In the Tromsø Study, alcohol units per occasion did not change much from 2001 to 2015, but the frequency of occasions consuming alcohol increased. Excessive alcohol use is a well-known risk factor for cognitive decline.[32] Studies have shown a J-shaped association between cognitive capacity and alcohol, suggesting a protective effect of moderate consumption and damage to the brain with excessive use.[23,32] A study from 2010 using data from the Tromsø Study suggested improved cognition with increasing wine intake within a moderate range. As alcohol consumption increases with income and educational level, the authors thought that their findings were due to residual confounding factors, despite adjustment for education.[33] Another study confirmed the findings, but explained the improvement in cognitive performance to be related to sex differences, as women drank more wine and men drank more beer and liquor, and women outperformed men in cognitive tests.[4] A cutoff at 21 >units per week has been suggested as a risk factor for dementia,[5] and a large meta-analysis concluded that people older than 60 years increased their dementia risks with more than 2 times per week.[34] The majority of the population in the Tromsø Study were at or below the advocated limit for harmful drinking[5,34] (Table 2). The moderately increased frequency of alcohol consumption in this study, however, was still strongly associated with the improved score on cognitive tests for both sexes. Confounding of not measured factors could be a possible explanation for this contradictory epidemiologic effect. Moderate alcohol consumption is also associated with higher education.[5,6] With increasing years of education, a higher cognitive capacity could make brains more resilient to the damaging effects of alcohol. Moderate alcohol consumption is also linked with being socially active,[35] and frequency of consuming alcohol could be a confounder marking social interactions. Using abstainers as the reference group could introduce a selection bias, as abstainers in some studies have shown poorer health compared with moderate consumers.[36]

Our analysis showed that physical activity was positively associated with cognitive test scores over birth cohorts, with a larger effect in men. It is recommended for people to be physically active to reduce the risk of cognitive decline.[37,38] Previous studies in the Tromsø Study, with 7 years between analyzed waves, have also found low physical activity to be associated with lower scores in cognitive testing, but only in women.[6] The positive effect of exercise in men in our study could be due to longer time of 14/15 years between the survey waves and a higher mean age. Our findings also comply with the same study on smoking, which had an inverse association with cognition in both sexes, and improvement in other cardiovascular risk factors such as hypertension and hypercholesterolemia to be only weakly associated with cognitive test scores.

With a large population of almost 10,000 people evaluated with 4 different cognitive tests covering different areas of cognition, and showing the same trends, the results are robust. The high attendance rate of 65% or higher in all 3 surveys ensures generalizability.[16]

The study included few excessive alcohol users and few with extreme obesity. It was not possible to make a variable for unit alcohol per week. This would have made the alcohol findings more comparable to the international literature. Participants were not asked about financial income in all survey waves.

In repeated testing, there could be introduced a learning bias. Reports on the subject are dissimilar. Some report an improved IQ score by 5–6 points[2]; others report a learning bias with mean test-retest interval of 47 days.[18] With longer test-retest intervals of mean 370 days, 1 study reports that

TAKE-HOME POINTS

- Later-born birth cohorts have better score on cognitive tests compared with earlier born in a population aged 60–87 years.
- In cognitive domains such as psychomotor ability, sustained attention, processing speed, episodic memory, and executive function, the improvement corresponded to 12 years for women and 10 years for men, indicating 70- to 72-year-olds in 2015/16 performed as 60-year-olds did in 2001.
- For short-term memory, the improvement was 10 years for both sexes. For long-term verbal memory, episodic memory, and the ability to use learning strategies, the test score improvement corresponded to 20 years for both sexes, indicating that for these domains, 80 is the new 60.
- The improvement was positively associated with increased education level, increased drinking frequency, increased physical activity, and, for men, smoking cessation and increased height.

reliability improved in a geriatric population.[17] Accordingly, we assume that the learning bias in our study, for the 37% that were tested more than once, will be very small as there is 15 years between testing.

Cognitive test scores were improved in the more recent born birth cohorts in all ages and in both sexes. The scale of these differences varied, but for some cognitive areas, 80 is the new 60. The improvement is positively associated with increased education level, increase in drinking frequency, increased physical activity, and, for men, smoking cessation and increased height.

Study Funding

Northern Norway Regional Health Authority (Helse Nord RHF) grant number: HNF1407-18.

Disclosure

The authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Publication History

Received by *Neurology: Clinical Practice* January 15, 2021. Accepted in final form May 21, 2021.

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Bjørn Heine Strand, PhD	Norwegian Institute of Public Health, Oslo	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Ieva Martinaityte, MD, PhD	Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø; Department of Medicine, University Hospital of North Norway, Tromsø	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Ellisiv B. Mathiesen, MD, PhD	Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø; Department of Neurology, University Hospital of North Norway, Tromsø	Drafting/revision of the manuscript for content, including medical writing for content
Henrik Schirmer, MD, PhD	Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø; Department of Cardiology, Akershus University Hospital, Lørenskog, Norway; Institute of Clinical Medicine, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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Received: 31 March 2023 | Revised: 8 August 2023 | Accepted: 22 August 2023

DOI: 10.1002/dad2.12479

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Incidence of dementia over a period of 20 years in a Norwegian population

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Funding information
Northern Norway Regional Health Authority, Grant/Award Number: RHF HNF1407-18; UiT The Arctic University of Norway

Abstract

INTRODUCTION: In Norway, the prevalence of dementia is higher than in demographically comparable, high income countries, but reliable incidence studies are lacking. This study calculated the incidence of age-specific dementia from 2000 to 2019.

METHODS: Participants from The Tromsø Study (n = 44,214) were included. Participants with a dementia diagnosis (n = 2049 cases) were identified. Poisson regression was used to calculate age-specific yearly and 5-year incidence rates from 2000 to 2019.

RESULTS: The incidence of dementia has decreased from 2000 to 2019. The trend was highly significant for ages of 60–99 years, and was similar for both sexes.

DISCUSSION: The incidence of dementia in North Norway has decreased over the past two decades similar to that in Western countries, indicating that the total prevalence is increasing due to an aging population. This decrease of incidence could introduce a reduction in future estimation of dementia prevalence.

KEYWORDS
dementia, incidence, Norway, prevalence

1 | INTRODUCTION

Dementia is a deadly neurodegenerative disease that affects cognitive function and behavior, has a significant impact on patients and their families, and is associated with a marked socioeconomic burden. It is associated with a wide range of health and social care needs, including long-term care services. Global burden of disease[1] estimated that worldwide 57.4 million of the older adult population experience dementia, and the prevalence is indicated to triple by 2050.[1,2] In 2019, dementia was the seventh leading cause of death worldwide according to the World Health Organization,[3] however, the second leading cause of death in high-income countries (HIC). In Norway, a HIC, dementia was the third leading death cause in 2021.[4] Knowledge of the future incidence and prevalence of this severe disease is important for planning health care resources and enabling health care systems to provide the best care and treatment for people with dementia and their families. A new report by Gjøra et al., after a rigorous study in 2020 has shown a higher prevalence in Norway, compared to similar countries.[5] The authors estimated that the prevalence numbers would double by 2050, and quadruple by 2100. However, they did not account for future incidence changes. Studies in the United States have already reported a decline in prevalence between 2000 and 2012.[6] A growing body of evidence suggests that the incidence of dementia is declining in Western countries,[6–8] although the global incidence is still 10 million yearly, with increase in Asia, the Americas and Africa, according to the 2015 World Alzheimer's Report.[2] The Alzheimer

Consortium reported in 2020 a decline in the incidence of dementia by 13% per decade in Europe and North America, more so in men than in women.[8] Similar declines in incidence have been found in other Scandinavian studies,[9,10] but incidence studies in Norway over time are lacking.

Although the prevalence of dementia is increasing due to longevity of the population and aging, known risk factors for dementia are improving, including cardiovascular risk factors and higher education.[11–15] Higher education has been shown to protect against dementia,[15] but has also been argued to only delay the onset due to increased cognitive reserve capacity in those with higher education.[16] Education levels have increased in HICs in the past century, especially among women.[14] Therefore, the secular trends in the incidence of dementia in the Norwegian population are of great interest. Our aim was to explore the time trends of incidence of dementia in a large Norwegian population over two decades.

RESEARCH IN CONTEXT

1. **Systematic review**: PubMed was used to review literature. Findings suggest an increase in incidence in Asia, America, and Africa. The incidence of dementia seems to be declining in Western countries, but there are great heterogeneity in samples and methods. Notably, there is a lack of longitudinal incidence studies in Norway. Dementia ranks as the third leading cause of death in Norway, and its prevalence has been found to be higher compared to similar countries.
2. **Interpretations**: In this study of a large community dwelling cohort followed for 46 years, our findings indicate a decline in the age-specific incidence of dementia over the past two decades. The trend was highly significant among individuals aged 60–99 years, and was observed in both males and females.
3. **Future directions**: The results in this large study implies a modification to the forecast of tripling prevalence of dementia over the next 30 years. The higher prevalence in Norway can likely be attributed to increased longevity, as incidence of dementia is declining

2 | METHODS

2.1 | Study design

The Tromsø Study is a community based longitudinal cohort-study. It was initiated in 1974 to investigate heart disease, but was later developed to include a broad variety of morbidities and risk factors. It has been repeated every 7–8 years and invited individuals from the municipality of Tromsø in North Norway, both previous and new participants, to respond to each survey. It has a high participation proportion of at least 65%.[17] For each survey, participants completed one or more questionnaires, underwent physical examinations, and laboratory tests.

2.2 | Study population

To calculate the incidence of dementia, participants from Tromsø1–7 were included (Figure 1). The inhabitants of Tromsø are mainly Caucasian, have access to a good, publicly funded health care system and free education, in an urban setting of approximately 77,000 inhabitants.

Endpoint data were retrieved from hospital records in the only hospital in the area, the University Hospital of North Norway, in the years 2000–2019. We identified patients who had previously participated in The Tromsø Study, and later were diagnosed with a dementia diagnosis. Using the International Statistical Classification of Diseases and Related Health Problems (ICD-10), coding Alzheimer's disease, vascular dementia, Lewy body dementia, Parkinson's dementia, and other specified and unspecified dementia diagnoses were included. The ICD codes and corresponding definitions are provided in the supplementary (table e-1).

We conducted a validation study with 150 patients, randomly chosen from each 5-year period up to the end of 2015. The records from each patient were manually reviewed to verify the diagnosis. To validate the registry from 2016 to 2019, we linked the registry to an ongoing multicenter study "The Norwegian registry of persons assessed for cognitive symptoms",[18] and we were able to validate additional 255 diagnoses from 2016 to the end of 2019. The diagnosis of dementia had high specificity (99%). The specificity of the subtype was lower (89%); therefore, we did not analyze the data set for the dementia subtypes.

2.3 | Ethics and approval

The study has been approved by the Regional Committee of Medical and Health Research Ethics in Norway (REK Sør-Øst, 2016/389) and the Data Protection Officer at University Hospital North Norway. Each participant signed a written informed consent. Consent to use the data in future research was also obtained.

2.4 | Statistical analysis

The Tromsø Study1–7 was linked to the dementia end-point registry. As we had few incident dementia cases ($n = 228$) before year 2000 and we wanted to include only new cases, we included participants who had their first dementia diagnosis registered in the hospital records from January 1, 2000. The diagnosis of dementia was dichotomized yes/no. The baseline for follow-up was the first date of participation in any Tromsø Study survey. If the first diagnosis of dementia was established

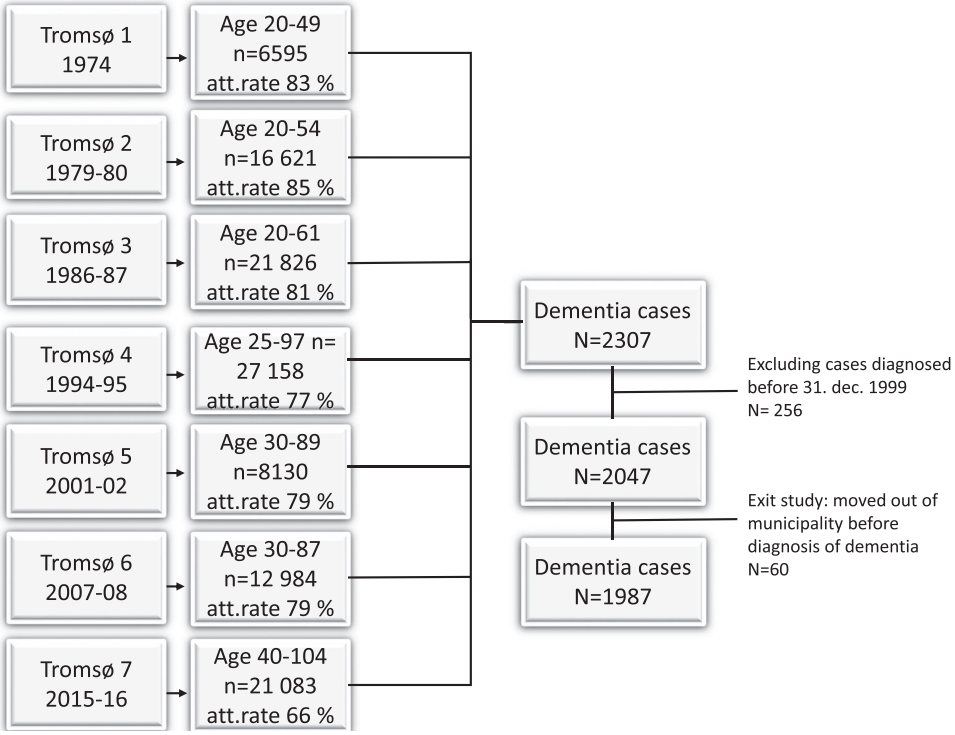

FIGURE 1 Flow chart of the participants by survey of The Tromsø Study 1–7.

before baseline, the participant was excluded. The exit date was set to the date of the first dementia diagnosis in hospital journals, the date of death, date of moving out of the municipality or the end of study; date December 31, 2019, whichever came first. The age at the start of the study was set at 1. July of the entry year minus the birthdate, divided by 365.25.

We generated a new observation for each participant for each calendar year from 2000, including age, time in years, and dementia status. We then made 10-year age groups from 50 years and older, and performed the following analysis on each age-group separately:

We used Poisson regression models to assess the association between calendar time and dementia incidence. Calendar time was modelled using fractional polynomials. The best-fitting model (out of 44 models) was determined using Akaike's information criterion. In separate Poisson models, calendar time was modelled as a categorical variable with indicator variables for each calendar year. All models were adjusted for age (Figures 2 and 3).

The incidence rate ratio was calculated by comparing the incidence in 2000 and the incidence in 2019 for each age group. To test for significant time trends, we used a likelihood ratio test that compared a model with and without calendar time.

To control for a small number of cases in annual rates within age groups, we combined calendar time into 5-year intervals and calculated incidence rates per 1000 person-years with 95% confidence intervals (CI) for each time and age group.

All analyses were performed using Stata version 17.0; StataCorp College Station, Texas, USA.

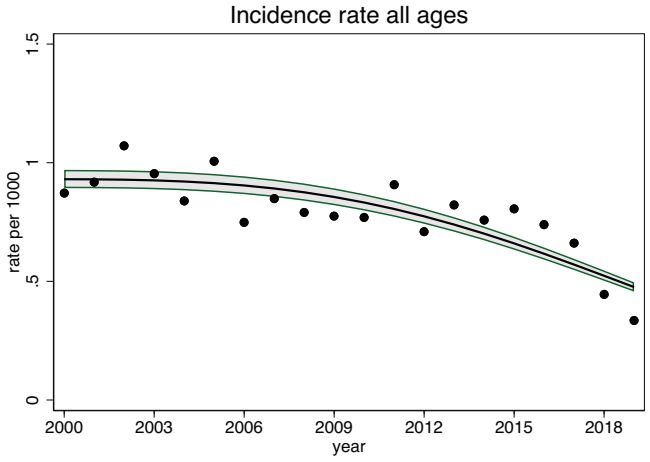

FIGURE 2 The age-adjusted annual incidence rate of dementia per 1000 person-years in participants from 50 to 99 years old. The black line indicates the mean, and the gray area shows the 95% confidence interval of the mean.

3 | RESULTS

3.1 | Characteristics of participants

A total of 44,214 participants were included in The Tromsø Study from 1974 to 2016. The baseline characteristics of the population are presented in Table 1. Of these, 2047 (58% women) developed dementia after 31 December 1999. The mean age for dementia diagnosis

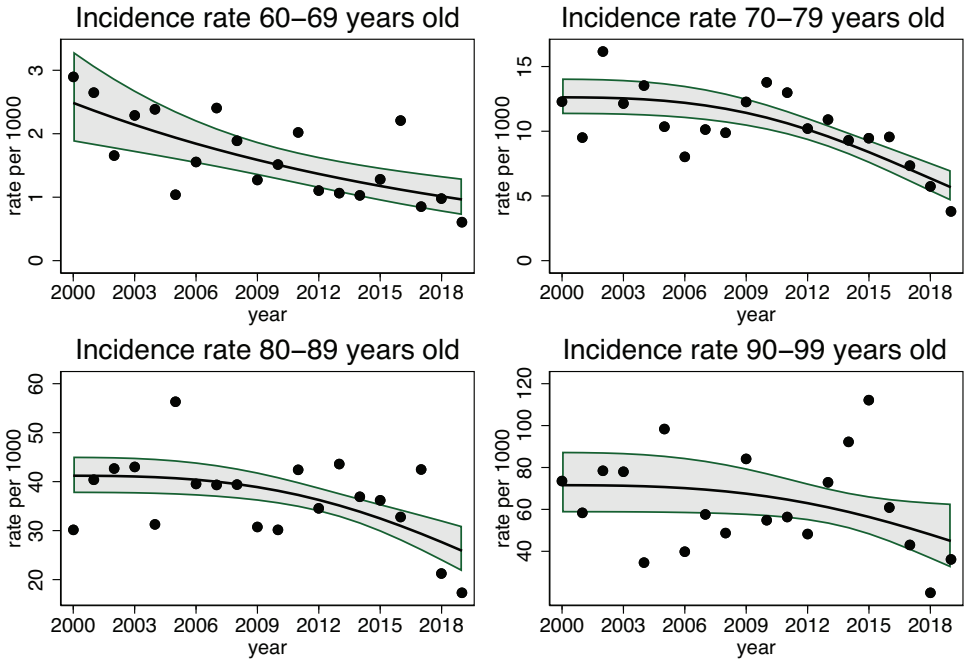

FIGURE 3 Age-adjusted annual incidence rate per 1000 person-years by age groups. The black line indicates the mean, and the gray area shows the 95% confidence interval of the mean.

was 81.5 (95% CI, 81.0–82.0) for women and 78.8 (95% CI, 78.3–79.3) for men. Person-years from year 2000 to the end of 2019 were 495,035. There were fewer men than women who developed dementia (874 men, 1205 women). Those who developed dementia, reported to be more inactive, had lower education level, had more hypercholesterolemia, and hypertension. They also reported more depression and anxiety (Hopkins symptom check list).

3.2 | Incidence

During a 20-year period, we found that incidence decreased in the entire sample aged 60–99 years, with no significant interaction between sex and time. The decrease was significant in each 10-year age group. For participants 50–59 years of age, there was no significant change in the incidence of dementia (Table 2).

4 | DISCUSSION

In this study of a large community-based cohort followed for 46 years, we found that age-specific incidence of dementia in 5-year time groups had decreased by up to 61% over the past two decades. The trend was significant in participants aged 60–99 years, and was similar for both sexes. This could introduce a modification to the forecast of a tripling prevalence over the next 30 years in both Norway and other comparable populations.[2,5]

To our knowledge, we are the first to report on the incidence of dementia over time in Norway. Our findings are similar to a study from the neighboring country Denmark, which used a registry of the entire national population,[10] over a similar time period (1996–2015). However, the study found an increase peaking in 2010, followed by a 2% annual decrease to 2015, along with a continuous increase in prevalence in all age groups, without birth cohort effects. They also found that the prevalence increased most among the older age groups, supporting the hypothesis that higher longevity is a partly cause of the increasing prevalence. A decrease first after 2010 was not seen in our study, suggesting a different development in Danish and Norwegian populations in regards to risk factor improvement.

Several other studies have shown the same decreasing incidence trends in dementia in those 60 years or older, supporting our findings. The Framingham Heart Study in the USA[7] found a 20% decrease in incidence per decade from 1977 to 2008 in participants 60 years or older without the peak seen in 2010 in the Danish population.[19] Sweden, found a 30% decrease in incidence in 1987–2004, in participants over 75 years of age.[9] Other studies compared two time points, such as the Rotterdam Study comparing dementia incidence in 1990 and 2000,[20] and found a decrease of 25% without statistical significance. A German study reported an incidence decrease between 2006 and 2009,[21] although 3 years of follow-up could be too short to conclude on a potential trend. Stronger trend findings can be found in the British studies, where a 20% decrease in incident dementia in people over 65 years of age was reported, between the two waves that occurred in 1990–1995 (CFAS I) and 2008–2013 (CFAS II).[22] Our study strengthens the findings of a decrease in age-specific incidence in western European and North American populations, where no studies have reported an increase in incidence over the past two or three decades.

We did not find any decrease in incidence for the population under the age of 60 years. Research on young-onset dementia epidemiology is scarce. A small incidence study from Norway included 89 cases under

TABLE 1 Participants from the Tromsø Study1–7; description at baseline; *p*-values, are calculated from chi-squared test, except for age calculated by t-test.

Variable	Total *N* = 44,214	Dementia free *N* = 42,167	Dementia cases *N* = 2047	*p*-Value
Age at participation	37.8 (14.1)	36.9 (13.4)	55.5 (16.7)	<0.001
Men	50% (22,068)	50% (21,214)	42% (854)	<0.001
Follow-up time	27.0 (13.8)	27.1 (13.8)	23.9 (12.1)	<0.001
Physical activity				<0.001
Inactive	29% (12,612)	28% (11,622)	48% (990)	
Active	51% (22,402)	52% (21,609)	39% (793)	
Very active	20% (8985)	21% (8726)	13% (259)	
Education				<0.001
7–10 years primary/secondary/technical school	25% (8794)	23% (7869)	63% (925)	
High school diploma (3–4 years)	28% (9766)	28% (9411)	24% (355)	
College/university, less than 4 years	20% (6980)	20% (6892)	6% (88)	
College/university, 4 or more years	28% (9716)	28% (9615)	7% (101)	
BMI-level				<0.001
< −18.5	2% (937)	2% (915)	1% (22)	
18.5–25	62% (27,010)	62% (25,970)	51% (1040)	
25–30	28% (12,167)	27% (11,415)	37% (752)	
30–35	7% (2945)	7% (2755)	9% (190)	
35–>	2% (810)	2% (777)	2% (33)	
Hopkins symptom check list				<0.001
No symptoms	19% (3318)	19% (3256)	7% (62)	
Some symptoms	51% (9019)	50% (8475)	62% (544)	
Sub-threshold symptoms	21% (3832)	21% (3643)	21% (189)	
Significant symptoms	9% (1670)	9% (1581)	10% (89)	
Smoking				<0.001
Yes, now	40% (17,821)	41% (17,067)	37% (754)	
Yes, previously	23% (10,064)	23% (9515)	27% (549)	
Never	37% (16,187)	37% (15,455)	36% (732)	
Other risk factors and comorbidity				
Living alone	36% (15,993)	36% (15,355)	31% (638)	<0.001
Hypertension	20% (8855)	19% (7911)	46% (944)	<0.001
Hypercholesterolemia	71% (31,170)	70% (29,246)	94% (1924)	<0.001
Stroke	1% (358)	1% (307)	3% (51)	<0.001
Diabetes	1% (592)	1% (532)	3% (60)	<0.001
Heart attack	1% (507)	1% (434)	4% (73)	<0.001

the age of 64 years who reported higher incidence rates compared to previous studies from other comparable countries, but did not assess incidence over calendar time.[23] A recent large meta-analysis reported that the global incidence rate of young-onset dementia was 11 per 100,000, corresponding to 370,000 new cases annually worldwide,[24] but here also incidence over time was not reported. The incidence of young-onset dementia in 2000–2014 from our data seems to be similar to that in the meta-analysis, but appears to be increasing to 32 per 100 000 in years 2015–2019. The reason of higher rates in our population may be due to that most young people with cognitive problems in the region are evaluated in our hospital, and may reflect more precise real incidence rates.

The secular trends of incidence are important for estimating the burden of dementia, since the prevalence of this disease increases with prolonged longevity and better health care.[25,26] Forecasts may be complicated as the modifiable risk factors for dementia also

TABLE 2 Five-year incidence rate per 1000 person-years by age group; The Tromsø Study.

Age group	50–59		60–69		70–79		80–89		90–99	
5-year group	IR/1000	95% CI	IR/1000	95% CI	IR/1000	95% CI	IR/1000	95% CI	IR/1000	95% CI
2000–2004	0.27	(0.14–0.52)	2.7	(2.1–3.6)	15.2	(13.1–17.5)	37.8	(32.8– 43.7)	63.5	(44.4–90)
2005–2009	0.26	(0.13–0.5)	1.4	(1.4–2.4)	12.0	(10.3–14.1)	41.4	(36.5–47.1)	63.9	(49.2–88)
2010–2014	0.2	(0.1–0.43)	1.2	(1.2–2.1)	12.7	(11.0–14.7)	39.4	(34.8–44.6)	66.4	(51.9–84.9)
2015–2019	0.32	(0.18–0.57)	1.1	(1.1–1.9)	7.7	(6.5–9.0)	30.1	(27.0—35.4)	52.8	(41.1-67.7)
Person years	139196		106049		58919		23531		3280	
IRR,										
2000 vs. 2019	1.0	(0.23–4.2)	0.39	(0.15–1.02)	0.45	(0.41–0.49)	0.88	(0.46–1.7)	0.63	(0.51–0.78)
Time-trend *p*-value	0.99		<0.001		<0.001		<0.001		0.04	

Abbreviations: IR, incidence rate; IRR, incidence rate ratio.

affects the estimates.[15] Though some of the risk factors, such as hypercholesterolemia,[27] hypertension, and smoking prevalence, are decreasing[13,15,28] and protective factors such as physical activity in leisure time[12,29,30] and education levels are increasing,[31] other risk factors such as the prevalence of diabetes and obesity are increasing.[29,32] However, overall improved risk factor levels in the population have already been shown to cause a decrease in incidence of stroke and myocardial infarction, and could also have contributed to the decrease in the incidence of dementia. As longevity increases due to the improvement of common risk factors for other deadly diseases, the prevalence of dementia, on the other hand, is still increasing, as Norwegian[5] and Danish studies[10] showed. However, the prognosis of the estimated future prevalence of dementia may have to be adjusted considering the decreasing incidence, as demonstrated in a study in England and Wales, where the estimated increase in prevalence was reduced by more than 50% over the next 20 years when the reduction in incidence was accounted for.[33]

4.1 | Strengths and limitations

This was a large follow-up study covering over 20 years with a large cohort and many cases, and the participation rate was high. The specificity for the diagnosis of dementia was high.

The study limitations included that the study was performed in a small geographical area with a homogenous population of mostly Caucasian people. As the endpoint registry only includes patients diagnosed or registered in hospital records or noted in death certificates, there may be unrecognized cases of dementia in the population. However, when merging with death registry, only six more cases appeared, and historically, dementia diagnosed in a hospital setting was required in the Tromsø municipality to be admitted to a nursing home. Accordingly, a majority of the dementia patients would have passed through a specialist evaluation at the hospital. Report or observation bias may also appear, as there is less focus on registering dementia diagnoses outside of geriatric / age psychiatric units.

5 | CONCLUSIONS

The incidence of dementia in Northern Norway has decreased over the past two decades for age groups 60-99, indicating that the observed increase in prevalence is due to an aging population and not an increase in the incidence of dementia. Accordingly, future prevalence estimates may have to be downscaled.

ACKNOWLEDGMENTS

This study was funded by the Northern Norway Regional Health Authority (Helse Nord RHF, HNF1407-18). UiT The Arctic University of Norway funded the article processing charge.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Data cannot be made public as legal restrictions are set by the Tromsø Study Data and Publication Committee in order to control data. To prevent possible reverse identification, any sensitive participant information was deidentified. The data can be made available from the Tromsø Study for researchers by the Tromsø Study Data and Publication Committee. Contact information: The Tromsø Study, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway; e-mail: tromsous@uit.no

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Johnsen B, Martinaityte I, Wilsgaard T, Schirmer H. Incidence of dementia over a period of 20 years in a Norwegian population. *Alzheimer's Dement*. 2023;15:e12479. https://doi.org/10.1002/dad2.12479

frontiers | Frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 15 June 2022
doi: 10.3389/fnagi.2022.906678

Leisure Time Physical Activities' Association With Cognition and Dementia: A 19 Years' Life Course Study

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Introduction: Cognitive impairment is one of the main disabilities in dementia. Physical activity (PA) has been suggested as protective for dementia. However, the findings are disparate in studies, and the question of whether this is because of reverse causality is still open. We aimed to explore the association of PA with cognition in people who later developed dementia compared to those who did not.

Method: Since 2001, 11,512 (55% women) participants over the age of 50 years had taken at least one cognitive test in the Tromsø Study. Of these, 1,123 (58% women) later developed dementia. The cases were extracted from hospital journals and entered into an endpoint registry. Leisure time PA (LTPA) was self-reported. Multilevel mixed-effects linear regression was used to address whether LTPA was associated with cognition, stratified by those later developing dementia, and dementia-free in a separate analysis.

Results: Leisure time PA was associated with scores in cognitive tests that were 55% (z-score 0.14) higher in those who did not develop dementia. For those in a preclinical phase of dementia, there was no association with LTPA on global cognitive scores. However, in a multifactorial test on processing speed and memory, women had a positive association with processing speed and memory.

Conclusion: Leisure time PA had a positive association with global cognition function only for those who did not develop dementia. In women who were developing dementia, LTPA had a positive association with processing speed and memory, while in men, there were no such associations.

Keywords: physical activity, dementia, cognition, cognitive, prevention

OPEN ACCESS

Edited by:
Yi Li,
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Reviewed by:
Greet Cardon,
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Specialty section:
This article was submitted to Alzheimer's Disease and Related Dementias, a section of the journal Frontiers in Aging Neuroscience

Received: *28 March 2022*
Accepted: *09 May 2022*
Published: *15 June 2022*

Citation:
Johnsen B, Strand BH, Martinaityte I, Lorem GF and Schirmer H (2022) Leisure Time Physical Activities' Association With Cognition and Dementia: A 19 Years' Life Course Study. Front. Aging Neurosci. 14:906678. doi: 10.3389/fnagi.2022.906678

INTRODUCTION

Dementia is a neurodegenerative disease that causes severe cognitive symptoms in a markedly increasing part of the world's older adults population (Livingston, 2020; Gauthier et al., 2021; GjOra et al., 2021). Physical activity (PA) is suggested as a preventive factor for dementia (Livingston, 2020), through substances such as brain-derived neurotrophic factor (BDNF)

(Tari et al., 2019), a neurotrophic and neuroprotective growth factor, which improves brain plasticity and induces neurogenesis and angiogenesis. A decrease in BDNF has been found in people with neurodegenerative diseases, and exercise has been shown to increase BDNF levels in the hippocampus which promotes learning and memory (El Hayek et al., 2019). However, meta-analyses of large observational studies have suggested that the effect of preventing dementia from PA is a reverse causality (Sabia et al., 2017a; Kivimaki et al., 2019). Several trials have aimed to improve cognition or prevent a decline in people with dementia using PA, but the evidence of positive effect on cognition from exercise programmes in people with prevalent dementia is scarce (Cardona et al., 2021). An umbrella review from 2020 found an effect on global cognitive function in patients with dementia, but no effect on attention, executive function, memory, motor speed, or language (Demurtas et al., 2020).

A large Cochrane review in 2015 reported that PA improved the ability to perform activities of daily living, but had no effect on cognition in people with dementia (Forbes et al., 2015). Furthermore, meta-analyses have shown that people with mild cognitive impairment have no significant increase in BDNF with exercise, even though there was a positive trend (Ruiz-Gonzalez et al., 2021). In older adults without dementia, exercise programmes have also failed to show an effect on cognitive outcomes (Sokołowski et al., 2021). However, those with high cardiorespiratory fitness at baseline, or those gaining high cardiorespiratory fitness, have shown improved cognitive abilities over a 5-year period (Sokołowski et al., 2021), suggesting that those without dementia pathology benefits from being physically active, which in turn gives high respiratory fitness over the last 4 decades. LTPA was first decreasing, whereas in the last 20 years, it was increasing for all age groups (Morseth and Hopstock, 2020), while occupational physical activity has been decreasing (Sagelv et al., 2020). These changes have been seen in the population at the same time as cognitive function and grip strength, as a measure of physical capability, and are reported to increase in later born birth cohorts (Strand et al., 2016; Johnsen et al., 2021).

We wanted to see how LTPA was associated with cognitive function in people who later developed dementia compared with those remaining dementia-free for up to 19 years. We hypothesised that a protective effect of PA for the prevention of dementia would result in less cognitive decline in the physically active people who later develop dementia compared to inactive. Alternatively, physical activity could be beneficial by improving cognition, without altering the rate of decline, thereby delaying the onset of dementia.

MATERIALS AND METHODS

The Tromsø Study

The Tromsø Study is an ongoing longitudinal study of the municipality of Tromsø, a city of 76,000 inhabitants in Northern Norway. The first survey was performed in 1974 (Tromsø1), and six more have followed (Tromsø2-7) until 2015/16, approximately 7 years apart (Jacobsen et al., 2012; Eggen et al., 2013). Since 2001, cognitive tests have been included. Representative samples or whole cohorts from the municipality were invited to each survey (Jacobsen et al., 2012; Eggen et al., 2013). They have all consented to the retrieval of medical events or death from hospital records and health registries.

Study Sample

Tromsø5-7 included 27,567 participants, of whom 1,326 later developed dementia. From these, we included 12,710 participants (1,123 later dementia cases) who had performed at least one cognitive test. As all of those who developed dementia were over the age of 50 at participation and because we wanted to see the effect on middle-aged and older adults, we excluded all participants under 50 years old at participation. This left a sample of 11,512 participants with the same frequency of dementia cases. To exclude prevalent dementia cases, those diagnosed with dementia before their first visit ($n = 21$) were excluded. Our final sample consisted of 11,491 participants (55% women). Of these, 1,102 (58% women) later developed dementia. The age range in the first survey was 50–98 years (**Figure 1** and **Table 1**). The maximum follow-up time was 19 years.

Dementia Register

We constructed a dementia endpoint register for the Tromsø Study (Tromsø1-7). Participants' national identity number was merged with the diagnosis register at the only hospital in the area, The University Hospital of North Norway. Dementia codes from the International Classification of Diseases-10 (ICD_10) coding Alzheimer's disease, vascular dementia, Lewy body dementia, Parkinson's dementia, and other specified and unspecified dementia diagnoses were included (**Supplementary Appendix Table 6**). The diagnoses were retrieved from the time period of 01.01.1986–31.12.2019. We identified patients whose initial diagnosis was changed over the course of the study period. The register was merged with the Norwegian Cause of Death Registry, but only additional cases were added.

A validation pilot was performed by one geriatric medical doctor (in training). ICD criteria were used to validate the diagnoses in prior medical records. A total of 150 patients, 50 randomly selected from each 5-year time period, from the year 2000 to 2015, were manually checked. Dementia diagnosis had high specificity (99%). The specificity of the subtype was lower (89%); therefore, we did not analyze the dataset for the subtypes of dementia.

The dementia registry was also merged with the ongoing study "The Norwegian registry of persons assessed for cognitive symptoms" (The Norwegian National Centre for Ageing and Health, 2021). Thus, 255 diagnoses for dementia register were validated from the year 2016, finding good consistency in dementia ICD codes.

Cognitive Tests in the Tromsø Study

A total of four cognitive tests have been performed in Tromsø5, Tromsø6, and Tromsø7. The fifth test (MMSE) was introduced in Tromsø6 and repeated in Tromsø7.

- Word test 1 (WT1), immediate recall, is a test of short-term verbal memory. For this test, 12 nouns were shown

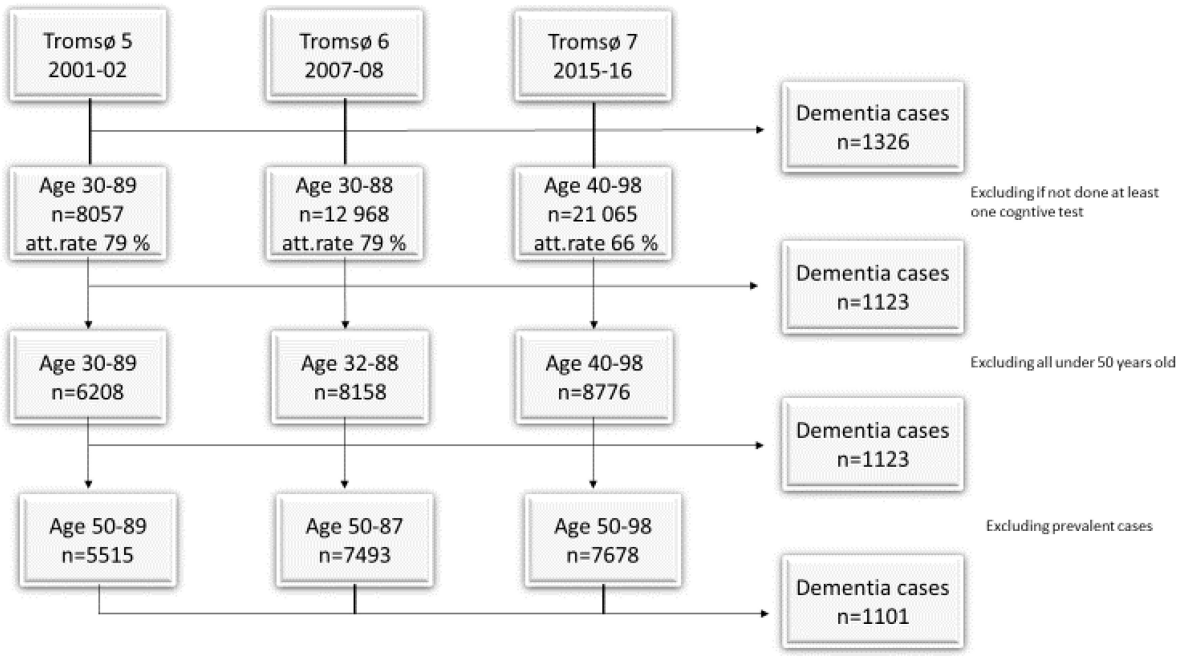

FIGURE 1 | The Tromsø Study 5–7, with survey year, age in years, attendance rate (att. rate), and number of cases (n).

on a board and read out loud at 5-s intervals. Points were given for each correctly remembered word within 2 min, 0–12 points.

- Word test 2 (WT2), recognition, is a test of long-term verbal memory, episodic memory, and the ability to use learning strategies. The 12 nouns from WT1 were mixed with 12 new nouns and shown with the same procedure. Participants were asked to identify each word as new or known. One point was given for each correctly identified word, 0–24 points.
- Digit Symbol Coding Test (DSCT), which is a part of the Wechsler Adult Intelligence Scale test battery (Wechsler, 2008), is used to examine psychomotor ability, sustained attention, processing speed, episodic memory, and executive function. It reveals small changes in cognition (Jaeger, 2018). Participants were given a sheet of numbered squares. On top of the sheet, nine symbols were paired with numbers. The subjects were asked to draw the symbol corresponding to the number without skipping a square. One point was given for each correctly identified symbol, 0–96 points.
- Finger Tapping Test (FTT), psychomotor speed. The participants were asked to tap on a plate as many times as they could. After a practice round, they did three rounds of tapping with the non-dominant hand. The points were the mean of the last three rounds, 1–96.
- The Mini-Mental State Examination (MMSE) was introduced in Tromsø6.

At least one cognitive test was performed by 11,491 people over the three surveys: 6,682 did only one, 3,637 did two, and 1,172 did all three. The tests were standardized to *z*-values to allow between-test comparability, and an individual mean score of the performed tests was used as a global cognitive score.

Measurement of Physical Activity

Leisure time PA was self-reported in two different questionnaires. In all participants under the age of 70 in Tromsø 5, and for all in Tromsø6-7, the Saltin–Grimby Physical Activity Level Scale was used (Grimby et al., 2015). This validated questionnaire had four different categories: inactivity, low, moderate, and vigorous activity (Morseth and Hopstock, 2020). Participants over 70 years old in Tromsø5 were asked two different questions about frequency of light (not sweating or out of breath) or hard LTPA (sweating or out of breath), yielding four categories (Kurtze et al., 2007; Morseth and Hopstock, 2020).

To include all participants in the same LTPA variable, we recoded both questionnaires to a new variable where 0 was inactive, 1 was active, and 2 was very active/athlete (refer to **Supplementary Appendix Table 1**). Sensitivity tests showed less difference in analysing SGPALS and the three categories of the new variable.

A validation study with participants from Tromsø6 found good correspondence between participants reported physical activity and physical activity objectively measured using an accelerometer (Actigraph LLC) and maximum uptake of O2 [VO_2(max)]. Correlation between self-reported PA and VO_2(max) was 0.40, $p < 0.001$ for women and 0.44, $p < 0.001$ for men. Intraclass correlation between accelerometer and self-reported LTPA was 0.62 for women and 0.59 for men (Emaus et al., 2010).

TABLE 1 | Baseline characteristics at first visit in the Tromsø Study.

	Total	Dementia-free	Dementia cases	*P*-value
	***N* = 11491**	***N* = 10389**	***N* = 1102**	
Age at first participation, mean (SD)	62.7 (7.7)	61.8 (7.3)	70.8 (6.4)	<0.001
Age at last participation, mean (SD)	74.4 (9.2)	73.7 (9.2)	81.1 (6.6)	<0.001
Men	45% (5218)	46% (4764)	41% (454)	0.003
Follow up time in years, mean (SD)	10.8 (5.5)	10.9 (5.5)	9.7 (4.9)	<0.001
Physical activity				<0.001
Inactive	29% (3197)	27% (2687)	51% (510)	
Active	55% (5992)	57% (5597)	40% (395)	
Very active	16% (1707)	16% (1619)	9% (88)	
Education				<0.001
7–10 years primary/secondary/technical school	32% (3534)	30% (2996)	53% (538)	
High school diploma (3–4 years)	30% (3296)	30% (2998)	29% (298)	
College/university less than 4 years	18% (2035)	19% (1941)	9% (94)	
College/university 4 or more years	20% (2271)	22% (2184)	9% (87)	
BMI-level in kg/m^2				<0.001
<18.5	1% (87)	1% (69)	2% (18)	
18.5–25	33% (3803)	33% (3417)	35% (386)	
25–30	45% (5168)	45% (4696)	43% (472)	
30–35	16% (1874)	16% (1687)	17% (187)	
35>	5% (522)	5% (485)	3% (37)	
Hypertension	45% (5072)	43% (4422)	61% (650)	<0.001
Stroke	3% (368)	3% (297)	7% (71)	<0.001
Diabetes	5% (521)	4% (445)	7% (76)	<0.001
Heart attack	6% (644)	5% (531)	11% (113)	<0.001
Smoking				0.07
Yes, now	22% (2460)	21% (2210)	23% (250)	
Yes, previously	44% (5059)	45% (4610)	41% (449)	
Never	34% (3876)	34% (3482)	36% (394)	
Living alone	24% (2759)	23% (2371)	35% (388)	<0.001
Mental status				0.98
No symptoms	35% (3660)	35% (3354)	35% (306)	
Some symptoms	39% (4050)	39% (3703)	39% (347)	
Sub-threshold symptoms	19% (1949)	19% (1786)	19% (163)	
Significant symptoms	7% (762)	7% (699)	7% (63)	

Description of participants at baseline (first visit), and in addition age at last visit and follow-up time. All values are in percent with n in parentheses if not stated otherwise. P-values obtained by Pearson's chi-squared test for categorical variables and the t-test for continuous variables.

Covariates

The covariates were chosen from lifestyle factors, including LTPA, education, and comorbidities which are suggested to affect the risk of dementia and cognitive decline (Livingston, 2020). As men and women had significantly different cognitive test scores in a previous study (Johnsen et al., 2021), we stratified the analyses on sex. Mediating factors included blood pressure, diabetes, hyperlipidemia, stroke, heart attack, smoking, mental status, and body mass index (BMI).

Questionnaires were given, and anthropometric measurements were collected during each survey (Eggen et al., 2013). Covariates were used from the same survey as the cognitive tests were done. Education was dichotomized into high and low education, where high education was university or college, and low education was primary education or high school as the highest degree. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg and/or use of antihypertensive drugs. Diabetes was a self-reported "yes/no" or the use of anti-diabetic drugs. Hyperlipidemia was defined as total serum cholesterol >5 mmol/l or high-density lipoprotein < 1.0 mmol/l for men; and <1.2 mmol/l for women, or low-density lipoprotein >3 mmol/l, or use of lipid-lowering drugs. Previous strokes and previous heart attacks were self-reported "yes/no." Smoking was self-reported as never, previous, or current. To assess mental status, we used the Hopkins Symptom Checklist-10 (HCSL-10), a questionnaire designed to measure physiological distress, anxiety, and depression (Strand et al., 2003). BMI was measured and categorized as underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5–25 kg/m^2), overweight (BMI = 25–30 kg/m^2), obese (BMI 30–35 kg/m^2), and severely obese (BMI > 35 kg/m^2).

Statistical Analysis

To visualize how education and physical activity were associated with cognitive scores, plots were constructed by calculating predictions for global cognitive function from a linear regression of global cognitive function on age. To measure the effect size between the groups that were dementia-free and participants who later developed dementia, we used Hedge's g for LTPA and the global cognitive test score.

To investigate the association between LTPA and cognitive abilities in those who later developed dementia compared to dementia-free, considering the repeated-measures design, multilevel mixed-effects linear regression was used. Models were fitted using the likelihood ratio tests. The time variable was calculated as time from participation in the Tromsø Study to dementia diagnosis, death, or study exit (31.12.2019), whichever came first.

Moderators were added successively, always including the independent variables PA and age in the model.

We first made four models see how different covariates affected the β-coefficients for activity, with a global cognitive score as the outcome. The models were as follows: Model 1: adjusted for age and time, Model 2: Model 1 + education, Model 3: full model, including Model 2, comorbidity, and lifestyle factors. To see whether different cognitive areas, as described under cognitive tests, were affected differently by LTPA, we also ran Model 2 on all cognitive tests separately. Interaction was tested by including the interaction term with age and PA, time and LTPA, sex and LTPA, and education and sex.

Sensitivity testing was done by excluding those who scored low on the cognitive tests to see whether possible prevalent dementia cases caused a lack of association between LTPA and cognitive test scores in those who later developed dementia. Possible prevalent cases were excluded. They were identified by an MMS score < 20 and a test score of 0 on any of the tests ($n = 489$). We also ran sensitivity tests, removing the lower 2.5 percentiles of scores, with no difference in significance and only small changes in beta values. However, n of dementia cases dropped to 897, as all observations for the participant are dropped.

All analyses were performed using Stata 17.0 MP.

RESULTS

Description

Mean age at first participation in the Tromsø Study was 61.8 for the dementia-free, and 70.8 for those who later developed dementia (**Table 1**). Mean age at first dementia diagnosis was 81.6 (CI 81.0–82.1) years for women and 80·5 (CI 79·9–80·1) years for men. Participants who later developed dementia were older at first survey, were less educated, and were less physically active. They were more likely to be hypertensive, have diabetes, report previous heart attack and stroke, and were more frequently living alone, but had the same level of anxiety and depression (**Table 1**). The Hedge's g measure for effect size between the groups of dementia/dementia-free was 1.07 for global cognitive function and 0.43 for LTPA. We found 2,307 individuals who had received one or more of these diagnoses in the full registry, and of these, 1,123 had previously performed at least one cognitive test in the Tromsø Study. A total of 568 patients with dementia diagnosis changed subtype of dementia from first to last visit.

Dementia-free participants scored higher on cognitive tests than participants who later developed dementia, and women scored on average better than men (**Figure 2**). The association was tested in regression models, including sex. Women out-tested men in Word test 1, Word test 2, the Digit Symbol Coding Test, and Mini-Mental State Examination, whereas men tested better than women in the Finger Tapping Test, all at $p < 0.001$.

Active dementia-free participants had a better global score on cognitive tests than inactive dementia-free participants did. For those who later developed dementia, being active did not improve their global cognitive test scores, even though there seemed to be a non-significant level difference for the active and inactive in this group as well. Inactive dementia-free women had a steeper decline in cognitive test scores with age compared to inactive, dementia-free men (p-interaction = 0.001). This interaction remained significant when adjusted for education. Inactive dementia-free participants of both sexes also had a steeper decline with age compared to active dementia-free participants ($p < 0.001$) (**Figure 2**). However, women still outperformed men ($p < 0.001$) if they remained dementia-free. There was no significant effect of sex on those who later developed dementia.

People of both sexes with high education had higher cognitive scores (**Figure 3**), compared to those with lower education levels. Participants in the preclinical phase of dementia had lower cognitive scores before the onset of dementia compared to dementia-free subjects with similar education. People with high education prior to dementia onset had similar cognitive test scores as dementia-free with low education at the same age. Men had a steeper decline in cognition if they were higher educated, and they developed dementia later than women in the same group. However, this slope was not statistically significant (p-interaction = 0.623). There was no overall significant interaction between education and activity level with cognitive tests as the outcome, but when tested separately, there was an interaction between education and activity in dementia-free women only.

Physically active participants scored better than those who were inactive on cognitive tests if they were dementia-free (**Table 2**). However, if they were developing dementia, higher activity levels were not associated with increased cognitive scores, except for short-term memory. Not adjusted for education, however, the difference in short-term memory was significant for very active women developing dementia. This association was no longer significant when education was included in the model. The positive association between LTPA and global cognitive score in dementia-free participants remained after adjusting for all covariates. When tested separately, adjusted for age, time, and education (**Table 3**), the results persisted, except for the tests Word test 1 and Digit Symbol Coding Test. For dementia-free women, the results on short-term memory (Word test 1) were solid ($p < 0.01$) before adjusting for education, but they

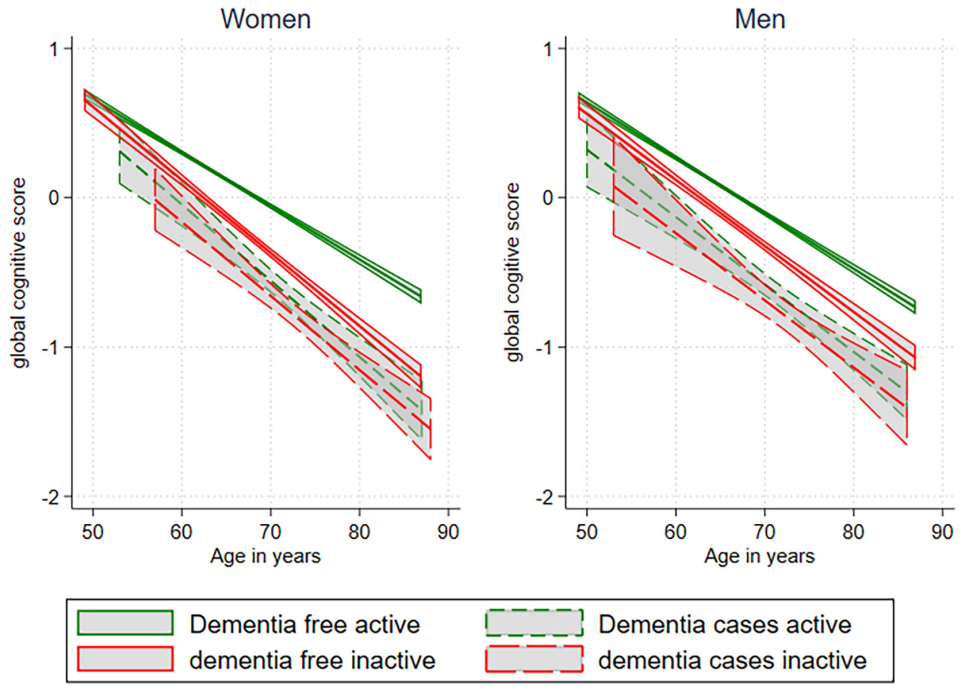

FIGURE 2 | Linear fit prediction plot for global cognitive score, stratified in activity, dementia, and sex.

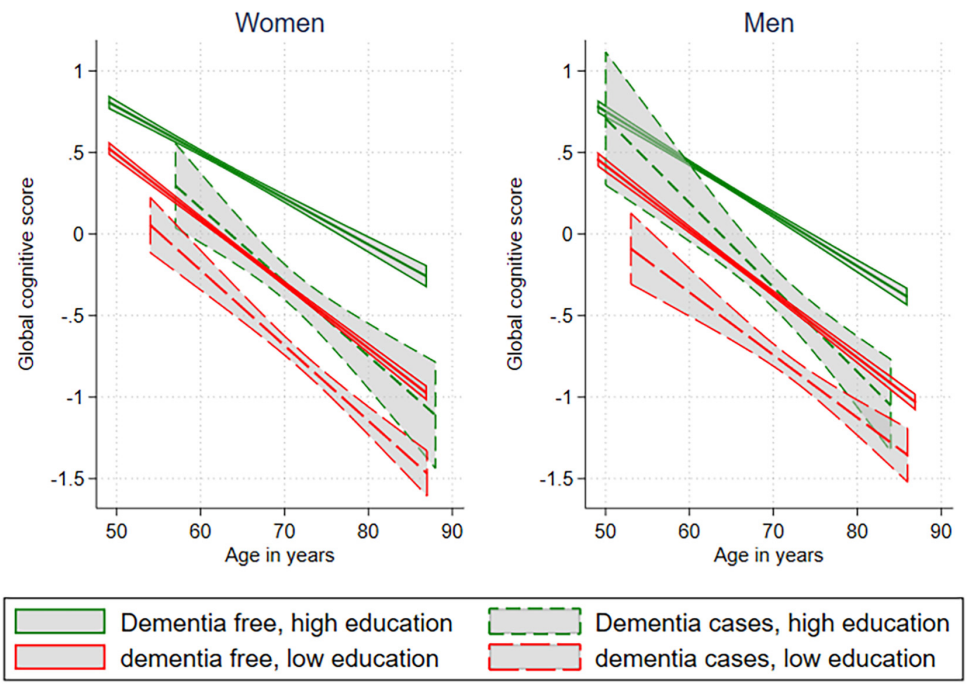

FIGURE 3 | A linear fit prediction plot for global cognitive score on age with a 95% confidence interval of the prediction, stratified on sex and education level. Only adjusted for age.

were non-significant after adjusting for this covariate. For the Digit Symbol Coding Test, the association remained statistically significant after adjusting for education for both groups, even those who later developed dementia. This relationship was present for both active and very active women, (respectively, $p = 0.003/0.002$) and for very active men ($p = 0.02$). The effect

TABLE 2 | Effect of PA on global cognitive score, mixed effects model.

	Women				Men			
***Z*-values**	**Dementia-free**		**Dementia cases**		**Dementia-free**		**Dementia cases**	
Global CF	**β**	**CI 95%**	**β**	**CI 95%**	**β**	**CI 95%**	**β**	**CI 95%**
Model 1								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.15**	(0.0.12–0.18)	0.04	(−0.07–0.15)	0.12**	(0.09–0.16)	0.03	(−0.09–0.14)
Very active	0.18**	(0.13–0.22)	0.26*	(0.06–0.46)	0.15**	(0.11–0.20)	0.09	(−0.07–0.25)
ICC	0.0.536	..	0.422	..	0.528	..	0.480	..
Model 2								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.12**	(0.08–0.15)	−0.01	(−0.12–0.10)	0.10**	(0.07–0.13)	0.02	(−0.10–0.13)
Very active	0.11**	(0.07–0.16)	0.17	(−0.03–0.37)	0.11**	(0.07–0.15)	0.05	(−0.11–0.22)
ICC	0.495	..	0.379	..	0.464	..	0.453	..
Model 3								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.09**	(0.05–0.12)	−0.05	(−0.17–0.06)	0.08**	(0.04–0.11)	0.02	(−0.10–0.14)
Very active	0.08**	(0.03–0.13)	0.14	(−0.08–0.36)	0.07**	(0.03–0.12)	0.02	(−0.15–0.18)
ICC	0.482		0.328		0.446		0.522	

*Multiple mixed linear regression with nested id and global cognitive test score outcome. Model 1: adjusted for time and age, Model 2: Model 1 + education, Model 3: Model 2 + comorbidity and life style factors. ICC, intraclass correlation *p < 0.05, **p < 0.001.*

also persisted in the sensitivity tests when those with very low scores were excluded. A positive association between LTPA and the cognitive score was not present in any other tests in those who later developed dementia.

Later born dementia-free women remember on average 0.8 and 1 word more in Word test 1 and Word test 2, than the later born (**Supplementary Appendix Table 5**). For men, these numbers are a little lower (0.6 and 0.9). Other tests have even more improvement, and the sex difference is significant. How these improvements play out in everyday life for participants is not an aim of this study, and therefore not tested, but it shows promise.

DISCUSSION

Leisure time PA was positively associated with global cognition only in those remaining dementia-free, and the results were indifferent to the choice of cognitive measurement. There was an increasing gap in cognitive scores with age between the active and inactive in the dementia-free group, a phenomenon not present in the group developing dementia. For them, cognitive scores progressed similarly with age across LTPA groups.

For women who later developed dementia, we found a different association with LTPA in Digit Symbol Coding Test. This is the test most sensitive to cognitive change, and it applies to working memory, processing speed, visuospatial processing, and attention (Wechsler, 2008; Jaeger, 2018). For women in the dementia group, these scores improved significantly for those who were active compared to those who were inactive. Only very active men had an association with LTPA on this cognitive test. Short-term memory also was improved in women developing dementia, but after adjusting for education, this association disappeared. This suggests that education is a strong mediator, as well as in people in a preclinical phase of dementia. An association with short-term memory was not present in men.

Our findings are comparable to findings in a prospective 5-year trial, where they used a different set of cognitive tests but tested the same cognitive domains as in our study (Sokołowski et al., 2021). High and moderate intensive training programmes had no effect on cognition in a dementia-free population, but there was a positive effect from high cardiorespiratory fitness at baseline. Our participants reporting high LTPA are accordingly likely to be more fit and have higher cardiorespiratory fitness. Thus, the positive effect on cognition may be driven through the same pathways in the brain, such as brain-derived neurotrophic factor. A decrease in brain-derived neurotrophic factor has been found in people with neurodegenerative diseases, and exercise has been shown to increase these levels in the hippocampus, promoting learning and memory (El Hayek et al., 2019). It has even been associated with a 2% increase in hippocampal volume (Erickson et al., 2011). Furthermore, an American umbrella review found some evidence of a larger effect of exercise in preventing dementia when the study samples included a higher percentage of women (Erickson et al., 2019). This is supported by our study, finding an effect of LTPA on some cognitive areas, even in women developing dementia. In men in the preclinical phase of dementia, LTPA had a weaker effect on these cognitive domains. This could be due to the highly sensitive qualities of the Digit Symbol Coding Test (Jaeger, 2018). For short-term memory, data from a large prospective cohort showed that women had better memory scores than men, and memory decline was faster for men than for women (Bloomberg et al., 2021). This was confirmed by our study, which showed a positive association between short-term memory and activity for both sexes. The novel

TABLE 3 | Mixed linear regression of activity impact on cognition with covariates.

	Women				Men			
	Dementia-free		Dementia cases		Dementia-free		Dementia cases	
z-values of	β	CI 95%	β	CI 95%	β	CI 95%	β	CI 95%
WT1								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.04	(−0.01–0.09)	0.07	(−0.07–0.21)	0.07**	(0.02–0.12)	0.02	(−0.15–0.19)
Very active	0.04	(−0.03–0.12)	0.19	(−0.07–0.45)	0.10**	(0.04–0.16)	−0.10	(−0.33–0.13)
ICC	0.37	..	0.26	..	0.391	..	0.287	..
WT2								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.10***	(0.05–0.15)	0.03	(−0.17–0.24)	0.10***	(0.05–0.16)	0.15	(−0.08–0.38)
Very active	0.07	(−0.00–0.14)	0.08	(−0.29–0.46)	0.11**	(0.04–0.18)	0.24	(−0.07–0.55)
ICC	0.33	..	0.364	..	0.288	..	0.493	..
DSCT								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.17***	(0.13–0.21)	0.14*	(0.01–0.27)	0.12***	(0.08–0.16)	−0.00	(−0.14–0.13)
Very active	0.16***	(0.10–0.22)	0.37**	(0.14–0.60)	0.13***	(0.08–0.18)	0.22*	(0.03–0.41)
ICC	0.574	..	0.363	..	0.652	..	0.395	..
MMSE								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.01	(−0.06–0.09)	0.13	(−0.45–0.71)	0.09**	(0.02–0.16)	0.49	(−0.37–1·34)
Very active	−0.03	(−0.12–0.07)	0.28	(−0.57–1·14)	0.08*	(0?00–0.16)	0.69	(−0.27–1·64)
ICC	0.335	..	0.255	..	0.38	..	0.188	..
FTT								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.12***	(0.08–0.17)	−0.12	(−0.28–0.03)	0.08**	(0.03–0.13)	−0.04	(−0.22–0.13)
Very active	0.21***	(0.14–0.27)	−0.01	(−0.29–0.27)	0.10***	(0.04–0.16)	−0.02	(−0.26–0.22)
ICC	0.61	..	0.397	..	0.591	..	0.61	..
Global CF								
Inactive	Ref	(-)	Ref	(-)	Ref	(-)	Ref	(-)
Active	0.12***	(0.08–0.15)	−0.01	(−0.12–0.10)	0.10***	(0.07–0.13)	0.02	(−0.10–0.13)
Very active	0.11***	(0.07–0.16)	0.17	(−0.03–0.37)	0.11***	(0.07–0.15)	0.05	(−0.11–0.22)
ICC	0.495	..	0.379	..	0.464	..	0.453	..

Multiple mixed linear regression with nested id and z-values of the five cognitive tests and global cognitive test score as outcome. All models are adjusted for age, time, and education. β *is the* β*-coefficient for active and very active, with inactive as reference. ICC, intraclass correlation. *p < 0.05, **p < 0.01, ***p < 0.001.*

finding in our study was that this association remained in women who later developed dementia. However, when adjusted for education, the relationship no longer reached statistical significance, suggesting that the effect of education makes the sex differences lesser.

A study in the United Kingdom has found sex and birth cohort differences. Men born earlier in the same cohort had better fluency scores than women, but the effect was reversed in later-born cohorts (Bloomberg et al., 2021). They argued that secular changes in education levels differed between sexes, and this was the basis for better performance in later-born women. Participants in our Norwegian study endured the same changes in education levels over the last decade. High education is known to be associated with higher cognitive performance, and it has been suggested to be the largest contributor to cognitive reserve (Stern, 2009). In addition, findings from a recent study suggested that physical activity was a modulator of cognitive reserve, explaining the discrepancy between the degree of cognitive impairment and brain imaging abnormalities in a group of older participants (average age of 81 years) (Sato et al., 2021). They tested several known risk factors for dementia, but only found leisure time activity and education to contribute to the cognitive reserve. The cognitive reserve theory (Stern, 2009) postulates that those with a high cognitive reserve do not escape dementia; their symptoms debut later and are more severe. This shows as a preventive effect in statistical analyses, and it could explain some of the overrepresentation of dementia in women, as our oldest women today have less education, and so lower cognitive reserve, than men born at the same time, concurrently outliving them. However, it is also possible that physical activity has a greater effect on the female brain, and that the Word test 1 and the Digit Symbol Coding Test are the only tests sensitive enough to capture it.

The MMSE results deviated from the ones of the other four tests. This could be due to lower n and shorter follow-up time, as it was performed only in Tromsø6 and Tromsø7. In addition, the MMSE has been suggested to be less sensitive in cognitively healthy people, as it probably has a ceiling and floor effect (Philipps et al., 2014). This might explain the findings in our presumably dementia-free or pre-onset dementia population.

Our study found that subjects with the same level of education, sex, and age had lower cognitive scores before the onset of dementia compared to the dementia-free subjects. Our findings

are similar to those from the Whitehall Study, where accelerating cognitive decline was observed 8–10 years before the onset of dementia (Sabia et al., 2017b).

The cognition-modulating impact of physical activity in healthy brains does not seem to have the same effect in the brains of males who later developed dementia as it does in female brains with subclinical dementia pathology.

However, compared to the inactive, those who have dementia-free brains and are active show increasing improvement in cognitive test scores with age. As a later dementia diagnosis cannot be predicted, health authorities should encourage physical activity to promote cognitive health in adults.

Strengths and Limitations

Strengths

This large population-based study with a wide age span and long follow-up generated over 1,000 dementia cases. Cognitive tests were performed up to 19 years before the onset of dementia, and information about baseline risk factors was available. The measurements and assessments were performed in a standardized manner.

Limitations

Physical activity was self-reported at baseline, but it showed good agreement with accelerometer-assessed activity (Morseth and Hopstock, 2020). The Saltin–Grimby scale does not allow to do dose-effect measurements, nor does it distinguish between different types of physical activity. The MMSE did not have good consistency with the other tests. Unfortunately, we did not have good measurements of hearing to include in this study.

The study included only dementia patients whose diagnoses were registered in hospital records. Furthermore, only few additional dementia cases were identified from death certificates, and it is possible that undetected later dementia in the non-case group would weaken our findings. We did not have access to the participants' APOE e4 status, but we did not analyze dementia subtypes either.

CONCLUSION

Physical Activity has a positive association with global cognition function only in healthy brains. However, if already in the preclinical phase of dementia, PA does not improve overall cognition. In the dementia-free, the gap between active and inactive increases with increasing age, favoring active dementia-free people. PA impacts cognitive domains in men and women differently, with a larger effect on women.

DATA AVAILABILITY STATEMENT

Data cannot be made public as legal restrictions are set by the Tromsø Study Data and Publication Committee to control data and prevent potential reverse identification of de-identified sensitive participant information. The data can be made available from the Tromsø Study for researchers at the Tromsø Study Data and Publication Committee. Contact information: The Tromsø Study, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway; e-mail: tromsous@uit.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Committee for Medical and Health Research Ethics (REK Helse Sør-Øst 2016/389). All participants consented to the retrieval of medical events or death from hospital records and health registries.

AUTHOR CONTRIBUTIONS

BJ: data curation, formal analysis, investigation, methodology, analysis tools, visualization, and writing – original draft. BS: funding acquisition, methodology, and writing – review and editing. GL: formal analysis, methodology, and writing – review and editing. IM: project administration, supervision, and rewriting – review and editing. HS: data curation, funding acquisition, methodology, project administration, analysis tools, supervision, and writing – review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

Helse Nord (grant number: HNF1407-18) funded the project. UiT The Arctic University of Norway funded the Article Processing Charge.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.906678/full#supplementary-material

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