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UNIVERSITY OF TURKU

SECULAR CHANGES IN CARDIOVASCULAR RISK FACTORS AMONG 70-YEAR-OLDS – EFFECT ON COGNITIVE IMPAIRMENT AND LONG-TERM CARE

Jenni Vire

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To my family

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JENNI VIRE: Secular changes in cardiovascular risk factors among 70-year-olds – effect on cognitive impairment and long-term care
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ABSTRACT

Cardiovascular diseases and dementia are major public health concern, and they share several risk factors. Dementia-related disorders are the primary cause for long-term care among older adults. By affecting potential modifiable vascular risk factors, it is possible to influence the incidence of dementia and thus prevent or postpone the need for long-term care.

This thesis examined secular changes in cardiovascular morbidity, risk factor profiles, and dementia risk indices between the 1920 and the 1940 birth cohorts of home-dwelling older adults at the age of 70 years. Additionally, the association with the Brief Dementia Risk Index and incidence of dementia during a five-year follow-up was assessed. Factors predicting need for long-term care were examined among the 1920 cohort, and the future need for long-term care was predicted among the 1940 birth cohort.

The 1940 birth cohort had lower cardiovascular disease morbidity, and their dementia risk and future need for long-term care were lower compared with the 1920 birth cohort. Of the cardiovascular risk factors, blood pressure and cholesterol values declined in the 1940 birth cohort, but the prevalence of diabetes and obesity increased compared with the 1920 birth cohort. The main predictors for need of long-term care were cognitive decline and reduced physical function. The Brief Dementia Risk Index predicted incident dementia during a five-year follow-up among the 1940 birth cohort.

The findings suggest that by influencing the modifiable risk factors for cardiovascular diseases and dementia, it is possible to reduce the need for long-term care. It is unclear if the increased use of cardiovascular medications will compensate the increased cardiovascular risk due to diabetes and obesity. Despite better general health and cognitive performance among the 1940 birth cohort, the predicted rates of future need for long-term care were high, especially at the ages of 85 and 90 years among those with impaired cognitive or physical function.

KEYWORDS: dementia, cognitive impairment, risk index, cardiovascular, long-term care, older people, older adults, cohort comparison.

TURUN YLIOPISTO
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TIIVISTELMÄ

Sydän- ja verisuonisairaudet sekä dementia ovat merkittäviä kansanterveydellisiä haasteita, ja niillä on useita yhteisiä riskitekijöitä. Dementiaan johtavat sairaudet ovat tavallisin syy iäkkäiden ympärivuorokautisen hoidon tarpeeseen. Vaikuttamalla sydän- ja verisuonisairauksien muokattaviin riskitekijöihin, voidaan vähentää dementian ilmaantuvuutta ja siten ehkäistä tai siirtää myöhemmäksi ympärivuorokautisen hoidon tarvetta.

Tämä väitöskirjatyö selvitti 70-vuotiaiden kotona asuvien turkulaisten sydän- ja verisuonisairauksien sairastavuuden, riskitekijöiden ja dementiariskin muutoksia. Tutkitut olivat syntyneet vuosina 1920 ja 1940. Lisäksi tutkimuksessa arvioitiin dementian riskilaskurin yhteyttä dementian ilmaantuvuuteen viiden vuoden seuranta-aikana. Ympärivuorokautisen hoidon tarvetta ennustavia tekijöitä tutkittiin vuonna 1920 syntyneiden 22 vuoden seurantatutkimuksessa. Näiden ennustekijöiden perusteella ennustettiin vuonna 1940 syntyneiden tulevaa ympärivuorokautisen hoidon tarvetta.

Vuonna 1940 syntyneillä oli vähemmän sydän- ja verisuonisairauksia, heidän dementiariskinsä oli matalampi ja ennustettu tarve ympärivuorokautiselle hoidolle tulevaisuudessa oli pienempi verrattuna 1920 syntyneisiin. Vuonna 1940 syntyneiden verenpaine- ja kolesteroliarvot olivat vuonna 1920 syntyneitä matalammat, mutta diabetes ja lihavuus olivat yleisempiä. Pitkäaikaishoidon tarvetta ennakoivat erityisesti kognition heikentyminen ja toistuvat kaatumiset. Lyhyt dementian riskilaskuri (BDRI) ennusti dementian kehittymistä vuonna 1940 syntyneillä 70–75 vuoden iässä.

Tämän väitöskirjatyön tulokset viittaavat siihen, että vaikuttamalla sydän- ja verisuonisairauksien sekä dementian muokattaviin riskitekijöihin, on mahdollista vähentää ympärivuorokautisen hoidon tarvetta. Toistaiseksi on epäselvää, tuleeko sydän- ja verisuonisairauslääkkeiden lisääntynyt käyttö kompensoimaan diabeteksen ja lihavuuden yleistymisen aiheuttamaa sydän- ja verisuonisairausriskin kohoamista. Huolimatta 1940 syntyneiden yleisesti paremmasta terveydentilasta ja kognitiosta, ympärivuorokautisen hoidon tarve tulee olemaan suurta erityisesti korkeassa iässä niillä, joiden kognitio tai fyysinen toimintakyky on heikentynyt.

AVAINSANAT: dementia, kognitiivinen heikentymä, riskilaskuri, sydän- ja verisuonisairaudet, ympärivuorokautinen hoito, ikääntyneet, kohorttivertailu

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Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
ANU-ADRI	Australian National University Alzheimer's Disease Risk Index
APOE	Apolipoprotein E
APP	Amyloid precursor protein gene
AUC	Area under the curve
BDRI	Brief Dementia Risk Index
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CARTS	Cerebral age-related TDP-43 with sclerosis
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHCS	Cardiovascular Health Cognition Study
CHD	Chronic heart disease
CHS	Cardiovascular Health Study
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CTE	Chronic traumatic encephalopathy
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
DSI	Dementia Screening Indicator
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
FHS	Framingham Heart Study
FINGER	Finnish geriatric intervention study to prevent cognitive impairment and disability
HALE	Healthy life expectancy at birth
HATICE	Healthy Ageing Through Internet Counselling in the Elderly

HDL	High-density lipoprotein
HF	Heart failure
HLY	Healthy life years at birth
HR	Hazard ratio
HRS	Health and Retirement Study
IADL	Instrumental activities of daily living
ICD	International Statistical Classification of Diseases and Related Health Problems
KP	Kungsholmen Project
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LDL	Low-density lipoprotein
LDRI	Late life Dementia Risk Index
LEB	Life expectancy at birth
LIBRA	Lifestyle for Brain Health score
MAP	The Rush Memory and Aging Study
MAPT	Multidomain Alzheimer Preventive Trial
MCI	Mild cognitive impairment
MMSE	Minimental state examination
MRF	Modifiable risk factor
NTB	Neuropsychological test battery
OR	Odds ratio
OSA	Obstructive sleep apnea
PA	Physical activity
PAD	Peripheral arterial disease
PREDIVA	Prevention of Dementia by Intensive Vascular care
PSEN	Presenilin gene
PUFA	Polyunsaturated fatty acid
RCT	Randomized controlled trial
RR	Relative risk
SALSA	Sacramento Area Latino Study on Aging
SD	Standard deviation
SPRINT	Systolic Blood Pressure Intervention Trial
SSRI	Selective serotonin reuptake inhibitor
TBI	Traumatic brain injury
TDP-43	Transactive response DNA-binding protein 43kD
TIA	Transient ischemic attack
TUVA	Turun vanhustutkimus (The Turku Elderly Study)
UTUVA	Uusi Turun vanhustutkimus (The New Turku Elderly Study)
VD	Vascular dementia
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Upmeier E, Vire J, Korhonen MJ, Isoaho H, Lehtonen A, Arve S, Wuorela M, Viitanen M. Cardiovascular risk profile and use of statins at the age of 70 years: a comparison of two Finnish birth cohorts born 20 years apart. *Age Ageing*, 2016; 45: 84-90.

II Vire J, Salminen M, Viikari P, Vahlberg T, Arve S, Viitanen M, Viikari L. Secular changes in dementia risk indices among 70-year-olds: a comparison of two Finnish cohorts born 20 years apart. *Aging Clin Exp Res*, 2020; 32: 323-327.

III Vire J, Salminen M, Viikari P, Vahlberg T, Arve S, Viitanen M, Viikari L. The association of the Brief Dementia Risk Index and incident dementia among Finnish 70-year-olds: a five-year follow-up study. *Gerontology,* 2021; 67: 441-444.

IV Salminen M, Vire J, Viikari L, Vahlberg T, Isoaho H, Lehtonen A, Viitanen M, Arve S, Eloranta S. Predictors of institutionalization among home-dwelling older Finnish people: a 22-year follow-up study. *Aging Clin Exp Res*, 2017; 29: 499-505.

V Salminen M, Eloranta S, Vire J, Viikari P, Viikari L, Vahlberg T, Lehtonen A, Arve S, Wuorela M, Viitanen M. Prediction of the future need for institutional care in Finnish older people: A comparison of two birth cohorts. *Gerontology*, 2018; 64: 19-27.

1 Introduction

Cardiovascular diseases (CVDs) and dementia are both a major global public health concern. In high-income countries, ischemic heart disease, Alzheimer's disease (AD) and other dementias, and stroke, are three leading causes of death among older people (World Health Organization, 2020). The incidence of both CVDs and dementia increases with aging, and the number of people with CVDs or dementia is projected to increase principally because of increasing life expectancy and declining rates of mortality (Ahmadi-Abhari et al., 2017; Tsao et al., 2023).

CVDs and dementia share several risk and protective factors (Leszek et al., 2021), and already at the beginning of 21st century it was known that several vascular risk factors are associated with dementia (Kivipelto, Helkala, Hanninen, et al., 2001; Kivipelto, Helkala, Laakso, et al., 2001). It has been estimated that up to 40% of all dementia-related cases could be prevented if currently known modifiable risk factors were eliminated at a population level (de Bruijn et al., 2015; Norton et al., 2014).

Dementia is considered as the primary cause of long-term care in older people (Andel et al., 2007; Cepoiu-Martin et al., 2016; Gaugler et al., 2007; Gnjidic et al., 2012; Hajek et al., 2015; Luppa, Luck, Weyerer, et al., 2010). In Finnish nursing homes, around 70% of the residents have a diagnosed dementia-related disorder, and altogether nearly 90% have cognitive decline (Finnish Institute for Health and Welfare, 2024). In addition, the financial impact of dementia is significant, as it leads to increased costs for societies, communities, and families. It also represents substantial human costs to individuals and families when it leads to loss of independence and high strain on caregivers. The main cost drivers in dementia are costs due to home-based long-term care and nursing home expenses (Quentin et al., 2010; Schaller et al., 2015). For example, in 2010, the costs related to long-term care for dementia disorders accounted for 75% to 84% of the total costs related to dementia disorders (Hurd et al., 2013).

Secular changes of CVDs and dementia affect to the need of long-term care in future. Population of Finland is one of the oldest in Europe (International Institute for Applied System Analysis, 2020) and due to increasing life expectancy, the population is ageing rapidly. Due to this demographic trend and higher incidence of chronic conditions such as dementia (Ansah & Chiu, 2022), the number of older people needing long-term care may increase rapidly. However, by preventing CVDs it is possible to affect prevention of dementia and need for long-term care.

Dementia risk indices are tools that quickly and efficiently combine information on known risk factors of dementia. The main goal is to identify individuals with a risk for dementia who can be referred for more frequent monitoring and early interventions to prevent or delay the onset of cognitive decline (Barnes & Yaffe, 2011). The first dementia risk score for prediction of the risk of late-life dementia was published in 2006 (Kivipelto et al., 2006). Since then, numerous prediction models have been developed for different population, for people with a diagnosed chronic condition (for example diabetes or head trauma), for use in primary health care, and for use in research settings (E. Y. Tang et al., 2015).

This thesis reviews and further complements the research dealing with cardiovascular and dementia risk factors, dementia risk indices, and long-term care. It is based on two separate population-based follow-up studies (The Turku Elderly Study and The New Turku Elderly Study), including two cohorts of 70-year-olds, born 20 years apart (in 1920 and 1940) and lived in the city of Turku, in Southwest Finland. Cohorts are compared in terms of their cardiovascular and dementia risk factor profiles. Association of the Brief Dementia Risk Index and incidence of dementia are examined in the 5-year follow-up among the 1940 birth cohort (The New Turku Elderly Study). Factors predicting need for long-term care among the 1920 birth cohort are examined in the 22-year follow-up study (The Turku Elderly Study), and the future need for long-term care is predicted among the 1940 birth cohort (The New Turku Elderly Study).

2 Review of the Literature

2.1 Aging world – trends in life expectancy

Worldwide, population is aging in both developed and developing countries. The global aging phenomenon is due to general population growth and decline in leading causes of mortality. Life expectancy at birth (LEB), the number of years that newborn is expected to live if current mortality rates continue to apply, reflects the overall mortality level of a population. The world average LEB has increased by more than 40 years since 1900. Estimates suggest that in the beginning of the 20th century the average LEB was around 30 years (Riley, 2005), in 2000 around 67 years, and in 2020 nearly 73 years (The World Bank, 2021; World Health Organization, 2021a). The differences in LEB between countries and continents are wide, but the tendency is similar. Table 1 shows how the average LEB has increased between 1900 and 2021 in the USA, in Europe, and in Finland. However, during the past decade (2010–2020) the increase of world average LEB has decelerated (World Health Organization, 2021a). In the USA, the LEB has even been stable (Kochanek et al., 2020) and in the European Union the gains in LEB have slowed down (Raleigh, 2019). At the beginning of the 2020s, mainly due to the COVID-19 pandemic, the life expectancy decreased worldwide (Schöley et al., 2022).

In an aging world, it is desirable that the extra years gained through increased longevity are spent in good health and independently. The healthy life expectancy at birth (HALE) is used to describe average number of years that people are expected to live in a state of self-assessed good or very good health by considering years lived in less than full health due to disease and/or injury. To prevent the burden of age-related diseases, such as atherosclerosis, cardiovascular diseases, hypertension, type 2 diabetes, and all-cause dementia, the HALE should increase at least at the same rate as LEB. Despite all the efforts and improvements in health care, the HALE has not globally kept pace with the total life expectancy. According to the World Health Organization, the global increase in LEB between 2000 and 2019 was 6.6 years and the increase in HALE was only 5.4 years (World Health Organization, 2021a). In the European Union, an indicator known as Healthy Life Years at birth (HLY) has been monitored since 2005, and it indicates the life expectancy without activity limitations. Due to methodological differences in data collection and cultural factors in reporting, HLY varies a lot among the European Union countries. At the national level, HLY is suitable for observing trends (Sihvonen et al., 2017).

Population of Finland is one of the oldest in Europe (International Institute for Applied System Analysis, 2020). Between 1900 and 2022, the population has more than doubled from 2,656,000 to 5,564,000. At the same time, the proportion of population aged 65 and older has increased from 5.3% to 23.3% and proportion of 85 years and older from 0.1% to 2.9% (Statistics Finland, 2023). In the 2010s, HLY has not enhanced in Finland. For women, in 2010, the average HLY was 57.9 years (69.6% of the LEB) and in 2019 it was 54.8 years (64.9% of the LEB). For men, the corresponding values were 58.5 years (76.3 % of the LEB) and 57.7 years (72.9% of the LEB) (Eurostat, 2021). Therefore, older Finns tend to live most of the additional years with activity limitations. Women still live longer than men do, although the gap in average LEB in the European Union and in Finland has narrowed down since 2000 (Raleigh, 2019). Instead, in Finland, the gender gap favours Finnish men in terms of HLY (Eurostat, 2021).

Table 1. The average life expectancy (years) at birth globally, in the USA, in Europe, and in Finland (Andersson & De Turk, 2002; Kochanek et al., 2020; Minino & Smith, 2001; Riley, 2005; Roser et al., 2013; Statistics Finland, 2022a; The World Bank, 2021; United Nations, 2019).

Year	Global	USA	Europe	Finland	Finnish men	Finnish women
1900	~ 30	47–49	42.7	41.7		
1950	46–48	68.2	62.0	65.5	~ 63	~ 69
1970	56.9	70.8	70.4	70.2	65.9	74.2
1980	61.2	73.7	71.3	73.6	69.2	77.8
1990	64.2	75.4	72.8	75.3	70.9	78.9
2000	66.8	76.9	73.4	77.6	74.1	80.9
2010	71.0	78.7	76.3	79.9	76.7	83.2
2019	73.4	78.9	78.6	81.6	79.2	84.5
2021	72.8	77.0	77.0	81.8	79.2	84.5

2.2 Cardiovascular diseases among older adults

Cardiovascular diseases (CVDs) are globally known as the leading cause of death (World Health Organization, 2020), and the aging population is particularly susceptible to CVDs. In the Global Burden of Diseases Study during the period 1990–2017, there was an overall downward trend in the CVD incidence and mortality rates (Amini et al., 2021). Although the age-standardized mortality rates due to CVDs has declined, the number of deaths due to CVDs has increased (Naghavi et al., 2017) mainly because of the increasing number of older people. In the USA, the prevalence of CVDs, including hypertension, coronary heart disease (CHD), heart failure (HF), and stroke, increases from about 54% in men and women 40–59 years of age, to 77% in population of 60–79 years of age, and to 85% among those aged 80 years or older (Tsao et al., 2023). Similarly, the incidence of CVDs, including CHD, HF, and stroke or intracerebral hemorrhage, increases from 4–10 per 1,000 person-years in adults aged 45–54 years to 65–75 per 1,000 person-years in adults aged 85–94 years (Lloyd-Jones et al., 2009; National Institute of Health, National Heart, Lung, and Blood Institute, 2006).

According to the FinHealth 2017 survey, hypertension is very common among older adults in Finland (Koponen et al., 2018). In that survey, 79% of men and 82% of women aged 65 years and over were hypertensive (i.e., systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or use of antihypertensive medication). Prevalence of common CVDs among Finns aged 60 years and over are presented in table 2. In Finland, the morbidity and mortality from CVDs have significantly decreased since the late 1960s (Jousilahti et al., 2016). Over the past decade (2010–2020), the age-standardized mortality from CVDs decreased almost 30% in both men and women (Statistics Finland, 2022c). Still nearly 19,000 Finns died of CVDs in 2021 (Statistics Finland, 2022b). The amount corresponds to one third of all deaths. The most common fatal CVD is coronary artery disease (CAD), which accounted for nearly 8,800 deaths in 2021 (Statistics Finland, 2022c). However, the median age of those who died from CAD has increased remarkably since the 1970s. While in 1971, the median age was 65 years for men and 73 years for women, in 2021 the corresponding ages were 79 and 88 years (Statistics Finland, 2022c).

Table 2. Prevalence (%) of CVDs in Finland among older adults (Koponen et al., 2018).

	60–69 years old	70–79 years old	80+ years old
Hypertension			
Men	74.3	79.4	79.8
Women	69.1	84.3	87.2
CHD			
Men	11.0	19.4	28.0
Women	4.2	10.5	26.3
HF (during the past 12 months)			
Men	5.3	11.3	23.7
Women	2.5	7.0	27.3
Stroke or intracerebral hemorrhage			
Men	6.3	9.1	16.3
Women	2.9	6.1	13.7

2.3 Dementia

Dementia is a chronic or persistent disorder of mental processes caused by brain disease or injury and marked by memory and/or other cognitive impairments, personality changes, and impaired reasoning. Dementia is not a specific or single disease. It is a syndrome characterised by impairment in memory, orientation, language, calculation, problem-solving, learning capacity, and judgement that is severe enough to interfere with daily life and independent function (Kane & Thomas, 2017). Deterioration in emotional control, social behaviour, or motivation commonly accompany the cognitive decline (Kane & Thomas, 2017).

Before the 18th century, terms such as amentia, imbecility, foolishness, stupidity, simplicity, cams, idiocy, dotage, and senility were used to name states of cognitive and behavioral deterioration leading to psychosocial incompetence (Berrios, 1987). Although dementia has been referred to in medical texts since antiquity, the word *dementia* is from the late 18th century. Latin word *demens* originally meant 'out of one's mind'. Until the 19th century, dementia included also mental illnesses and any type of psychosocial incapacity. For the first time amentia and senile dementia were separated in 1838. The current concept of dementia formed during the 19th and the early 20th centuries. Based on histopathological examinations, it was possible to identify the most significant dementia disorders (Berrios, 1996).

The most common causes of progressive or primary dementias are Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Especially older people have a combination of several neuropathological changes, i.e., mixed dementia (Alafuzoff & Libard, 2024; Wharton et al., 2023). Secondary dementias or dementia-like symptoms may be treatable. These include for example nutritional deficiencies, certain types of medications, metabolic and endocrine abnormalities, infections and immune disorders, and heavy alcohol use (Little, 2018).

Dementia-related disorders are classified by using either The International Statistical Classification of Diseases and Related Health Problems (ICD) published by the World Health Organization, or The Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association. Currently in 2024, in Finland, healthcare uses predominantly the 10th version of ICD (ICD-10), which was endorsed already in 1990 (World Health Organization, 2012), and it has been used in Finland since 1996 (Finnish institute for health and welfare, 2011). The latest 11th version (ICD-11) was released in 2019 and came into effect on 2022 (World Health Organization, 2024), but is not yet in use in Finland. The latest 5th edition of DSM (DSM-5) was introduced in 2013 (American Psychiatric Association, 2013).

The definition of dementia has been updated in both the ICD-11 and the DSM-5. In the ICD-10, definition of dementia is etiological and described as a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions. Diagnostic guidelines emphasized decline in both memory and thinking, and impaired processing of incoming information. In the ICD-11, dementia-related disorders are called "Neurocognitive disorders". An important change in the classification is the possibility to include the etiology with the clinical character of the disorder, its characteristics, and some dominant symptoms.

In the DSM-5, dementia is called "Major Neurocognitive Disorder". While the DSM-IV criteria for dementia required the presence of memory impairment, together with deficit in one other cognitive domain, the new term focuses on the decline from a previous level of functioning as opposed to a deficit. The DSM-5 criteria for dementia outlines two core features of major neurocognitive disorder. The first is cognitive decline in one or more cognitive domains (attention, executive function, memory, learning, language, perceptual motor or social cognition), and the second is impairment that interferes with the patient's independence in everyday functioning. Thus, the new definition of dementia also removes the emphasis on memory impairment as it is known that memory impairment is not the first domain to be affected in all the diseases that cause dementia.

The effect of diagnostic criteria on dementia prevalence has been studied for example in Sweden (Wetterberg et al., 2024). They compared DSM-III-R, DSM-IV, DSM-5, ICD-10, and ICD-11 in two cross-sectional population-based studies of systematically selected 85-years-olds. The prevalence of dementia varied from 20.5% (ICD-10) to 32.9% (DSM-5) and 36.4% (ICD-11). Thus, the choice of diagnostic criteria has a large effect on the estimated prevalence of dementia.

In Finland, clinical diagnosis of AD is based on recommendations of the International Working Group updated in 2021 (Dubois et al., 2021), diagnosis of vascular dementia is based on criteria of NINDS-AIREN from 1993 (Román et al., 1993), diagnosis of dementia with Lewy bodies is based on criteria of DLB Consortium from 2017 (McKeith et al., 2017), and diagnosis of frontotemporal dementia is based on criteria from 2011 (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Overall changes in diagnostic criteria have focused on facilitating early diagnosis and moving to a more direct etiological diagnosis based on various biomarkers (e.g., neuroimaging, cerebrospinal fluid markers, and blood-based markers). In terms of AD, a purely biological definition that relies on biomarkers has also been proposed (Jack et al., 2018) enabling diagnosis of AD even before symptom onset.

2.3.1 Epidemiology of dementia before the 21st century

The first epidemiological studies concerning dementia were carried out during the 1960s and 1970s in Scandinavia and Great Britain (Fratiglioni et al., 1999). The Finnish Social Insurance Institution carried one of the first nationwide population study of the prevalence of dementia out in Finland in 1977–1981 (Sulkava et al., 1985). Even before that, the epidemiology of dementia was studied in the city of Turku (Mölsä et al., 1982). During the 1980s, epidemiological methods were used to describe different patterns of dementias, and to identify risk factors for different dementia-related disorders. In the late 20th century, follow-up studies on incidence and etiology of dementia were finally initiated (Fratiglioni et al., 1999).

The prevalence of dementia is the percentage of a population that is affected with dementia at a given time. The incidence of dementia in contrast is the number of new dementia cases that developed during a specific period. The prevalence is determined by incidence and duration of disease. Changes in the prevalence of dementia between cohorts may be due to differences in treatment, level of awareness of cognitive disorders, but mostly due to changes in diagnostic criteria over time. For example, eight different criteria have been proposed for AD in research settings since 1984. These criteria have varied according to clinical and biological requirements (Dubois et al., 2021). Especially in the first epidemiological studies, the variation in age-specific prevalence between study populations was wide. There were potentially real differences, but more likely the variation was due to methodological differences (Mortimer et al., 1981).

In the 1970s and 1980s in Western countries, the prevalence of moderate and severe dementia among people aged 65 and over varied from 1.3% to 6.2%, and that of mild dementia from 2.6% to 15.4% (Henderson, 1986; Mortimer et al., 1981; Schoenberg, 1986). The all-cause dementia prevalence increased with age almost exponentially, and nearly doubled every five years (Fratiglioni et al., 1999; Hofman et al., 1991; Jorm et al., 1987; Rocca et al., 1991). The worldwide prevalence rates of dementia are shown in table 3.

The number of dementia incidence studies was very limited during the 1970s and 1980s. Most of the data is from Sweden, Central Europe, and Great Britain, where the incidence rates were reasonably similar in the 65–84 age group. Among 85 years old and older, the incidence rates instead varied a lot. Based on the studies made between 1966 and 1997 in Europe, in the USA, and in the East Asia, the incidence rose with age linearly, with no tendency toward a leveling off in old age. For AD, the rise in incidence was nearly linear, but for VD considerable variability across studies made it difficult to find out clear trends. The predicted age-specific incidence rates of at least mild dementia in Europe in the 1990's are shown in table 4.

The prevalence rates of moderate to severe dementia in Finland in the 1980’s are shown in table 3. The annual incidence of all types of dementia for people aged 65 years and older was 0.4% (Mölsä et al., 1982).

2.3.2 Epidemiology of dementia in the 21st century

During the 2000s and 2010s, dementia has become a global public health concern. Research has expanded to identify risk factors of dementia, and completely new neuropathological entities, e.g., limbic-predominant age-related TDP-43 encephalopathy (LATE) and cerebral age-related TDP-43 with sclerosis (CARTS) which are both linked to transactive response DNA-binding protein 43kD (TDP-43) (de Boer et al., 2020; R. I. Mehta & Schneider, 2023; Wharton et al., 2023). Dementia-related disorders are increasingly investigated in developing countries, but the number of prevalence studies in high-income countries has decreased. Worldwide, the number of people with dementia is projected to increase principally because of increasing life expectancy and declining rates of mortality (Ahmadi-Abhari et al., 2017). In 2015, according to World Alzheimer Report, around 50 million people worldwide had dementia, and the number is projected to triple by 2050 (Prince et al., 2015). Estimates of dementia prevalence in people aged 60 years and older varied from 4.6% in Central Europe to 8.7% in North Africa and Middle East (Prince et al., 2015).

Dementia prevalence rates in Europe estimated by the Alzheimer Europe in 2019 are shown in table 3. Compared with Alzheimer Europe’s former project European Collaboration on Dementia (EuroCoDe) from 2006–2008, the prevalence rates have decreased for both sexes in age groups above 80 years (Alzheimer Europe, 2019). In 2021, approximately 150,000 Finns had diagnosed memory disorder (Roitto et al., 2024), but it is estimated that approximately 200,000 Finns have some form of cognitive disorder (Memory disorders. Current Care Guidelines 2023., n.d.). In 2040, the overall number of Finns with diagnosed dementia-related disorder will be around 250,000 (Roitto et al., 2024).

The incidence rates of dementia in Western Europe and in Finland are shown in table 4. In Finland, every year approximately 23,000 people contract dementia (Roitto et al., 2024). Results regarding time trends in dementia incidence in Europe suggest declining rate over the past decades. For example, in Sweden, from the late 1980s to the 2010s, the incidence of dementia in people aged 85 years and over seems to have decreased (Wetterberg et al., 2023). In Germany, during the early 2000s, the trend has been similar among older adults aged 65 years and over (Doblhammer et al., 2015). In addition, a meta-analysis of European and North American studies found declining incidence rate of dementia between 1988 and 2015 in people aged 65 years and over (Wolters et al., 2020). On the other hand, in a more recent study from the United Kingdom, incidence trends varied by age group between 1999 and 2018 (Stevenson-Hoare et al., 2023). In that study, the incidence of dementia decreased in those aged 60 years and under, had no significant change in those aged 60–79, but increased in those aged 80 years and over.

Table 3. Worldwide prevalence of dementia (Africa excluded due to low number of studies) in the 1990's (Fratiglioni et al., 1999), prevalence of dementia in Europe in 2018 (Alzheimer Europe, 2019), prevalence of moderate to severe dementia in Finland in the 1980's (Sulkava et al., 1985), and prevalence of dementia in Finland in 2021 (Roitto et al., 2024).

Age range	Worldwide prevalence in 1990's	Prevalence in Europe in 2018	Prevalence in Finland in the 1980's	Prevalence in Finland in 2021
65–69	1.5	1.3	4.2[b]	3.1[b]
70–74	3	3.3		
75–79	6	8.0	10.7[c]	14.0[c]
80–84	12	12.1		
85–89	33-68[a]	21.9	17.3[d]	41.2[d]
≥90		40.8		

[a] Estimate for those aged 85 years and over. Based on the pooled data from Europe, North America and Asia.
[b] Age range 65–74 years old
[c] Age range 75–84 years old
[d] Age range 85 years old and over

Table 4. Dementia incidence/1,000 person years in Europe in 1990's (Jorm & Jolley, 1998), in Western Europe in 2015 (Prince et al., 2015), and in Finland in 2021 (Roitto et al., 2024).

Age range	Incidence in Europe in 1990's	Incidence in Western Europe in 2015	Incidence in Finland in 2021
65–69	1.1	5.3	5.9[a]
70–74	3.1	9.3	
75–79	7.0	17.3	24.6[b]
80–84	10.7	32.0	
85–89	16.3	57.0	50.8[c]
≥90	29.7	122.4	

[a] Age range 65–74 years old
[b] Age range 75–84 years old
[c] Age range 85 years old and over

Mortality related to dementia and Alzheimer's disease has increased during the past decades. The growth in the number of deaths from dementia is in part the result of more specific diagnostics and changes in the WHO guidelines for recording causes of death. Globally, deaths due to dementia-related disorders more than doubled between 2000 and 2019. Dementia disorders were the seventh leading cause of global deaths in 2019 compared to 14th in 2000. In high-income countries, deaths due to Alzheimer's disease and other dementia-related diseases have overtaken stroke and were the second leading cause in 2019 (World Health Organization, 2020). In Finland, dementia is the second most common cause of death among people aged 75 and over, and the third common cause among the total population (Official Statistics of Finland, 2021b). In 2021, altogether 11,500 Finns died from dementia including Alzheimer's disease (Statistics Finland, 2022b).

2.4 Risk factors related to dementia and cardiovascular diseases

Dementia and cardiovascular diseases (CVDs) are common among older people, and they share several risk and protective factors (Leszek et al., 2021). In high-income countries, ischemic heart disease, Alzheimer's disease (AD) and other dementias, and stroke, are three leading causes of death among older people (World Health Organization, 2020). As the root causes of AD are still unknown, there is robust evidence supporting the hypothesis that CVDs may contribute to AD progression (Deckers et al., 2017; Fillit et al., 2008; Stampfer, 2006; Wolters et al., 2018). Studying the relationship between CVDs and AD is complicated. These diseases often coexist and research diagnostic criteria for AD often exclude patients with cerebrovascular diseases (Dubois et al., 2014), although cerebrovascular diseases can even independently lead to the dementia (Skrobot et al., 2017, 2018). The relationship between CVDs and AD is complex because they share common risk factors. It is also possible that CVDs directly or indirectly are involved in the pathogenesis leading to AD (Brain et al., 2023). It is also unclear which CVDs consistently increase dementia risk.

Risk factors of dementia and CVDs can be divided into the non-modifiable and potentially modifiable risk factors. Non-modifiable risk factors include age, gender, race/ethnicity, genetic, and family history. Potentially modifiable risk factors are related to lifestyle and certain medical conditions (Livingston et al., 2020; Ngandu et al., 2015; Rosenberg et al., 2018). The significance of individual risk factors varies during the life course. In terms of late-life dementia, low level of education is the most important risk factor in the early life (<45 years). In midlife (45–65 years), hypertension, obesity, excessive alcohol consumption, hearing loss and traumatic brain injury are relevant risk factors. And in later life (>65 years), depression, smoking, physical inactivity, diabetes, social isolation, and air pollution may increase dementia risk. Some late-life risk factors possibly have a bidirectional impact. This means that a risk factor may increase the likelihood of subsequent disease, but the same factor may also be affected if the disease is already present. For example, depression might be a risk for dementia, but in later life, dementia might cause depression (C.-C. Liu et al., 2023). Similarly, obesity and hypertension in midlife increase the risk for future dementia, but in later life lower weight and decreasing blood pressure might signify illness rather than an absence of risk (Abell et al., 2018; Delgado et al., 2018; Kivimäki et al., 2018; McGrath et al., 2017; Singh-Manoux et al., 2018).

Preventing dementia depends on risk reduction of potentially modifiable risk factors. It is estimated that around 40% of worldwide dementias could be prevented or delayed by influencing modifiable risk factors (Livingston et al., 2020). However, most research data is from high-income countries and there is only limited evidence of the impact of risk factors in low- and middle-income countries (Anstey et al., 2019). Prevalence of dementia in low- and middle-income countries is rising faster than in high-income countries due to increase in life expectancy and greater exposure to risk factors. For example, smoking is rising in China while falling in most high-income countries (Hoffman et al., 2019). Therefore, the potential for dementia prevention is even higher in low- and middle-income countries than in global estimates.

The following risk factors are commonly related to CVDs and dementia: age, hypertension, diabetes, dyslipidemia, obesity, physical inactivity, smoking, and alcohol consumption. In the next sections, these risk factors related to dementia and to the relationship between dementia and CVDs are discussed in more detail. In addition, genetic factors, depression, social contacts and loneliness, hearing impairment, and traumatic brain injury related to dementia are discussed.

2.4.1 Age, gender, and ethnicity

Age is the strongest risk factor for all-cause dementia and CVDs, but dementia and CVDs are not an inevitable consequence of ageing. For example, in the Finnish Vitality 90+ study the prevalence of dementia among people aged 90 years and over was around 40% (Jylhä et al., 2019). Almost 80% of dementias occur in people aged 75 years and older (Carone et al., 2014) and concerning CVDs the prevalence in older adults is considerably higher than in the population aged 60 years and under (Benjamin et al., 2019). Historically, it has been thought that women are at greater risk of developing dementia, because almost two-thirds of patients with AD dementia are women. The sex difference in the prevalence of dementia has been explained by women’s higher life expectancy, but this explains the difference only partly. There are also differences related to e.g., tau pathology with earlier onset and faster progression of cognitive decline in women (Buckley et al., 2019, 2020), but the exact mechanisms are still unclear. It has also been suggested that 1) the effect and/or frequency of modifiable risk factors varies between men and women (e.g., smoking, and traumatic brain injury are more common among men, and women have had less access to education); 2) some risk factors have a stronger effect in one sex or another (e.g., *APOE* genotype or other genetic variants located on autosomal chromosomes); and 3) some risk factors are restricted to one sex (e.g., pregnancy, oophorectomy, prostate cancer and androgen deprivation therapy) (Mielke, 2018; Rocca et al., 2014). For the present, it is unclear whether gender alone is a risk for dementia.

With respect to CVDs, the gender differences that lead to discrepancies in CVD risk factors and outcome are largely due to sex hormones and their associated receptors (Garcia et al., 2016). The decline of sex hormones has been shown to play an important role in the development of CVDs with advanced age, in both men and women (Araujo et al., 2011; Garcia et al., 2016). Nevertheless, most cardiovascular risk factors affect women differently from men, leading to different disease profiles in men and women (Lam et al., 2019; Oneglia et al., 2020). For example, in Finland women are more likely to develop heart failure, while CHD and stroke are more prevalent in men (Koponen et al., 2018).

Results from studies concerning race and ethnicity and risk of dementia have been inconsistent. In 2021, Alzheimer's Association concluded that older Black and Hispanic Americans are disproportionately more likely than older White Americans to have AD or other dementias, but many studies suggest that after adjusting for health and socioeconomic risk factors, no difference in AD prevalence exist. Instead, Black, and Hispanic populations are disproportionately affected by chronic health conditions (e.g., CVDs and diabetes), lower levels and quality of education, higher rates of poverty, and greater exposure to adversity, that are associated with higher dementia risk ("2021 Alzheimer's Disease Facts and Figures," 2021). In terms of CVDs, there is consistent evidence that ethnic groups including Black, Hispanic, American Indian, Asian, and other minority groups in Western high-income countries are at a higher risk of CVDs (Lip et al., 2007). Nonetheless, this excess risk is largely attributable to historical and current socioeconomic inequalities and cultural factors rather than genetic differences (Pearce et al., 2004). Studies in the USA have shown that people of color experience varying degrees of social disadvantage that puts these people at increased risk of CVDs.

2.4.2 Hypertension

Findings regarding CVDs and dementia risk have been inconsistent, especially in the case of hypertension at different stages in the life-course (Sierra, 2020), but research suggests that hypertension in mid-life is associated with an increased risk of late life dementia. The population attributable risk of hypertension for dementia is estimated to be nearly 16%, and hypertension diagnosed at the age of 30–44 has the highest age-specific global attributable fraction for dementia compared to older population (Mulligan et al., 2023). A systematic review and meta-analysis of 209 prospective studies found moderate-quality evidence that midlife hypertension was related to a 1.19- to 1.55-fold excess risk of cognitive disorders (Ou et al., 2020). In the Framingham Offspring cohort comprising 1440 people (mean age 55 years at baseline) and follow-up over 18 years, the risk of developing dementia was elevated (HR 1.6, 95% CI 1.1 to 2.4) if blood pressure (BP) in midlife was ≥140/90 mmHg (McGrath et al., 2017). In the same cohort, people in late midlife (mean age 62 years) with ideal cardiovascular parameters (current non-smoker, BMI 18.5–25 kg/m^2, regular physical activity, healthy diet, BP <120/<80 mmHg, total cholesterol <5.2 mmol/l, and fasting blood glucose <5.6 mmol/l) and those with at least one of these risks were compared (Pase et al., 2016). People with ideal cardiovascular parameters had a lower 10-year risk of all-cause dementia (HR 0.8, 95% CI 0.1 to 1.0), vascular dementia (0.5, 0.3 to 0.8), and AD (0.8, 0.6 to 1.0). It is notable, that increased blood pressure during midlife followed by a rapid decrease in blood pressure in later life is associated with, and potentially caused by, dementia development (Abell et al., 2018; McGrath et al., 2017; Walker, Sharrett, et al., 2019).

The Systolic blood pressure intervention trial – memory and cognition in decreased hypertension (SPRINT-MIND) was the first trial to suggest the effect of intensive BP control on risk of dementia (Williamson et al., 2019). It was a pre-planned sub-study of the original SPRINT trial. At the baseline, 9,361 hypertensive adults aged 50 years and older (mean age 67.9 years) but without diabetes or history of stroke were randomized 1:1 to either a systolic BP goal of less than 120 mmHg (intensive treatment group, *n*=4,678) or less than 140 mmHg (standard treatment group, *n*=4,683). The trial was conducted in the United States and Puerto Rico. The median intervention period was 3.3 years, and total median follow-up 5.1 years. The intervention included diet, physical activity, components of a healthy lifestyle (e.g., reduction of alcohol consumption, cessation of smoking, healthy BMI, and low cholesterol), and antihypertensive medication(s). Intensive BP control (target of less than 120 mmHg) compared with a standard treatment did not significantly reduce the incidence of probable dementia (7.2 vs 8.6 cases per 1,000 person-years; HR 0.83; 95% CI 0.67 to 1.04). However, intensive treatment of systolic BP significantly reduced the occurrence of mild cognitive impairment (14.6 vs 18.3 cases per 1,000 person-years; HR 0.81; 95% CI 0.69 to 0.95).

At least five meta-analyses of BP medications to lower high BP have found reduced risk of dementia or cognitive impairment (Ding et al., 2020; D. Hughes et al., 2020; Hussain et al., 2018; Lennon et al., 2023; Tully et al., 2016). For example, in the meta-analysis of Hughes et al, blood pressure lowering with antihypertensive medication compared with control was significantly associated with a lower risk of incident dementia or cognitive impairment [7.0% vs 7.5% of patients over a mean trial follow-up of 4.1 years; OR 0.93 (95% CI, 0.88 to 0.98); absolute risk reduction 0.39% (95% CI, 0.09% to 0.68%)]. A 2020 meta-analysis of over 50,000 participants in 27 studies focused on different antihypertensive drugs and risk of dementia. They found no consistent relationship by antihypertensive medication class with incident cognitive decline or dementia (Peters et al., 2020).

2.4.3 Diabetes

Diabetes in later life is associated with an increased risk of dementia (Ahtiluoto et al., 2010; Chatterjee et al., 2016; G. Cheng et al., 2012; Profenno et al., 2010). For example, in a pooled meta-analysis from over 2.3 million participants with type 2 diabetes across 14 cohort studies, type 2 diabetes was associated with an increased risk of any dementia (RR 1.6, 95% CI 1.5 to 1.8 for women and 1.6, 1.4 to 1.8 for men) (Chatterjee et al., 2016). It is also known that the risk of dementia increases with the duration and severity of diabetes (Barbiellini Amidei et al., 2021; Roberts et al., 2008), and that poor glucose control has been associated with greater cognitive decline (Yaffe et al., 2012). Presence of diabetic complications, such as hypoglycemic events, microvascular complications, and CVDs, in patients with type 2 diabetes are also associated with increased dementia risk (Bruce et al., 2014; Exalto, Biessels, et al., 2014; B. Zheng et al., 2021). The effect of different diabetic medications on cognition or dementia risk is still inconsistent (C. Cheng et al., 2014; McMillan et al., 2018). In 2017, a Cochrane review found no impact on cognitive decline or dementia, when they compared intensive vs standard diabetes control RCTs with a five-year follow-up (Areosa Sastre et al., 2017).

Diabetes often co-exists with other cardiometabolic diseases (X. Cheng et al., 2022). People with at least two cardiometabolic diseases [type 2 diabetes, heart disease (ischemic heart disease, heart failure or atrial fibrillation) and stroke] have double the risk of developing dementia (Dove et al., 2023). In the Swedish National Study on Aging and Care a total of 2,500 healthy, dementia-free adults aged 60 years and over were followed up for 12 years. The speed of cognitive decline was accelerated if participant had more than one cardiometabolic disease. With a greater number of diseases, the magnitude of the risk was even greater (Dove et al., 2023).

2.4.4 Dyslipidemia

The association between total cholesterol and risk of dementia seems to vary with age and follow-up (Anstey et al., 2008, 2017; Hersi et al., 2017; Prince et al., 2014; World Health Organization, 2019). Some studies have showed no association or an inverse association with total cholesterol levels measured in later life. On the other hand, studies examining the effect of mid-life total cholesterol levels in longer follow-up have reported a positive association. In a meta-analysis of seventeen studies (1.2 million participants) midlife (age <65 years) dyslipidemia was associated with increased incidence of mild cognitive impairment and all-cause dementia in later life (Wee et al., 2023). In this meta-analysis, a mean age at baseline ranged from 42.4 to 56.7 years and the follow-up from 7 to 36 years (median 21.2 years).

The interplay between hypertension, dyslipidemia, and cognitive function is complex (Akasaki & Ohishi, 2023), and hypertension and dyslipidemia frequently coexist (Al Zamili et al., 2019; Niklas et al., 2019). The estimated prevalence of lipitension (presence of hypertension and dyslipidemia in one person) has varied a lot between studies, from 15% to 88%, but lipitension is more common among older population (Chobanian et al., 2003; Eaton et al., 1994; Gebrie et al., 2018; Grinshtein et al., 2021; Jamerson et al., 2008; Naghavi et al., 2017; O'Meara et al., 2004; Z. Xu et al., 2020). In the National Health and Nutrition Examination Survey III conducted in 1988–1994 in the USA, 64% of participants with hypertension also had dyslipidemia and, conversely, approximately 47% of participants with dyslipidemia had hypertension (Devabhaktuni & Bangalore, 2009). Overall, it is suggested, that higher levels of HDL cholesterol and diastolic BP may have a protective effect on the brain and cognitive function in community-dwelling older adults with hypertension and dyslipidemia (Akasaki & Ohishi, 2023).

Possible mechanism behind the association between blood lipids and dementia is related to oxysterols (e.g., 24- and 27-hydroxycholesterol), which can pass the blood-brain barrier (Loera-Valencia et al., 2019). In clinical studies, higher levels of 27-hydroxycholesterol have been found in both cerebrospinal fluid (Leoni et al., 2004; Mateos et al., 2011; Wang et al., 2016) and brain tissue (Heverin et al., 2004; Testa et al., 2016) of AD patients compared to controls. Randomized trials have examined the effect of statins in prevention of cognitive decline or dementia. So far, no evidence has been found, but trials have been limited by the duration of follow-up (<5 years) (McGuinness et al., 2016). There is some evidence that statins in younger people, those in earlier stages of dementia, and those with *APOEe4* allele might modify cognitive function (G. Li et al., 2010; Rockwood et al., 2002; Sparks et al., 2006).

2.4.5 Obesity

Overweight and obesity has been an emerging concern during the last decades (Chooi et al., 2019; D. M. Nguyen & El-Serag, 2010), as worldwide obesity has nearly tripled since 1975 (World Health Organization, 2021c). WHO defines overweight for adults as a BMI greater than or equal to 25 kg/m^2, and obesity as BMI greater or equal to 30 kg/m^2 (World Health Organization, 2021c). Despite the large body of evidence about the pathophysiological link between obesity and CVDs, obesity has been considered for a long time a minor risk factor compared to other well established CV risk factors, such as hypertension, diabetes, and dyslipidemia. Only in 2021, obesity has been acknowledged as a recurrent, chronic non-communicable disease (Burki, 2021).

Current evidence supports the relationship between obesity and dementia. A systematic review and meta-analysis of 19 longitudinal studies including nearly 600,000 people aged 35 to 65 years and followed up for up to 42 years showed that obesity (but not overweight) at mid-life increases the risk of dementia (RR 1.3, 95% CI 1.1 to 1.6) (Albanese et al., 2017). Although there is some evidence that weight loss is associated with improvement in cognitive function the data about the long-term effects of weight loss in preventing dementia are absent (Veronese et al., 2017). On the other hand, being overweight in older adults could be more protective than normal weight in terms of overall mortality (Flicker et al., 2010), and being underweight in both late-mid-life and old age might be associated with a higher risk of dementia (Anstey et al., 2011; Qizilbash et al., 2015). Nevertheless, the latter might be explained, at least in part, by reverse causality.

2.4.6 Physical inactivity

Physical activity (PA) is related to brain health, and PA seems to have beneficial effects on brain structures (Rovio et al., 2010). Other potential mechanisms underlying the association between PA and risk of dementia are most likely indirect. For example, PA has positive effect on obesity, hypertension, insulin resistance and high levels of cholesterol (Chieffi et al., 2017; World Health Organization, 2019). Additionally, in older adults without dementia, physical exercise improve balance and reduce falls (Papalia et al., 2020), improve mood (Blake et al., 2009), and reduce mortality (Fukushima et al., 2024).

The studies of PA are complex. Exercise routines change with age, and differ across sex, social class, and cultures. In previous meta-analyses of longitudinal observational studies with follow-up even decades, exercise has been associated with reduced risk of dementia (Hamer & Chida, 2009; Sofi et al., 2011). Later meta-analysis of 19 prospective observational cohort studies with more than 400,000 people (mean age 45.5 years) initially free of dementia examined the association between dementia and physical inactivity when reverse causation bias was considered (Kivimäki et al., 2019). They found no association between all-cause dementia or AD and physical inactivity, when PA was measured more than 10 years before dementia onset. When measured less than 10 years before dementia diagnosis, physical inactivity was associated with increased incidence of all-cause dementia (HR 1.40, 95% CI 1.23 to 1.71) and AD (1.36, 1.12 to 1.65). They also found that physical inactivity was associated with increased risk on incident diabetes (1.42, 1.25 to 1.61), coronary heart disease (1.24, 1.13 to 1.36), and stroke (1.16, 1.05 to 1.27). In addition, a subgroup of physically inactive individuals who developed cardiometabolic disease had excess risk of dementia.

Despite the promising findings on longitudinal cohort studies, RCTs of exercise interventions for cognition in healthy older adults have been less successful. This may be caused by bias related to decline in PA during the prodromal stage of dementia. This period might be even 10 years, and during this time physical inactivity might be either a consequence or a cause or both in dementia.

Overall, according to WHO guidelines, PA has a small, beneficial effect on normal cognition, and it should be recommended to adults with normal cognition to reduce the risk of cognitive decline. Even in adults with mild cognitive impairment, there is low quality evidence that PA interventions have a positive effect on cognition (World Health Organization, 2019). So far, the effect of specific types of exercise on dementia risk is unclear.

2.4.7 Smoking

Smoking has vascular and toxic effects, and it increases air particulate matter (van der Lee et al., 2018). Tobacco is a major risk factor for several medical conditions, and smokers are at a higher risk of premature death than non-smokers and they may die before dementia occurs (World Health Organization, 2021b). In terms of research concerning the association between smoking and risk of dementia, this causes uncertainty and bias (Chang et al., 2012; Debanne et al., 2007). However, plenty of evidence from observational studies indicate an association between smoking (including in mid-life) and dementia, or cognitive decline, in later life (Beydoun et al., 2014; Di Marco et al., 2014; Durazzo et al., 2014; Lafortune et al., 2016; North et al., 2015). In respect of CVDs, tobacco smoking was identified as a major risk factor already in the 1960s (U.S. Public Health Service, 1971).

Evidence from experimental intervention trials of tobacco cessation is limited. Given the high population attributable risk and all harmful health outcomes of tobacco, the WHO have made a strong recommendation about the interventions to treat tobacco dependence (World Health Organization, 2019). Stopping smoking, even when older, reduces the risk of dementia. In a Korean study of around 46,000 men aged 60 years or older and followed-up for eight years, long-term quitters (stopping smoking for more than 4 years) and never smokers had decreased risk of all-cause dementia compared with continual smokers (HR 0.9, 95% CI 0.8 to 1.0 and 0.8, 0.7 to 0.9, respectively) (Choi et al., 2018).

2.4.8 Excessive alcohol consumption

Excessive alcohol consumption is associated with changes in brain structures, cognitive impairments, and an increased risk of all types of dementia (Rehm et al., 2019; Topiwala et al., 2017). For example, in a French 5-year (2008–2013) retrospective cohort study of over 31 million hospital patients, the alcohol use disorders (harmful use or dependence as defined in ICD) were associated with increased dementia risk for both women and men (women HR 3.3, 95% CI 3.3 to 3.4, men 3.4, 3.3 to 3.4). The relationship of dementia with alcohol use disorders was particularly clear in the earlier onset (people aged less than 65 years) dementias (Schwarzinger et al., 2018).

Light to moderate alcohol consumption in middle to late adulthood has been associated with a decreased risk of cognitive impairment and dementia in numerous observational studies (Hersi et al., 2017; Ilomäki et al., 2015; Lafortune et al., 2016; W. Xu et al., 2017). Due to methodological limitations, causality of this association could not be established (World Health Organization, 2019). However, a U-shaped relationship between alcohol consumption and dementia and/or cognitive impairment is the most consistent pattern. It links particularly excessive alcohol consumption to a significantly increased risk of dementia (W. Xu et al., 2017).

A threshold of brain safety alcohol consumption (quantity and frequency) is still ambiguous. In the meta-analysis of Xu et al, the lowest risk (RR≈0.9) was at around 6g/day. In the same study, the all-cause dementia risk seemed to be elevated (≈10%) when the alcohol consumption exceeded 23 drinks/week or 38g/day (W. Xu et al., 2017). On the other hand, the Ginkgo Evaluation of Memory Study found no significant association with a lower risk of dementia among older adults with or without mild cognitive impairment (MCI) at baseline when alcohol intake was within recommended limits (up to 14 drinks/week). They also found, that among participants without MCI, daily low-quantity drinking was associated with lower dementia risk compared with infrequent higher-quantity drinking (Koch et al., 2019). The UK Whitehall study with 23 years follow-up, included 9,087 participants aged 35–55 years at baseline (1985/1988). They found that abstinence in midlife was associated with higher risk of dementia (HR 1.47, 95% CI 1.15 to 1.89) compared with consumption of 1–14 units/week. Among those drinking more than 14 units per week, a 7-unit increase in alcohol consumption was associated with a 17% (95% CI 4 to 32) increase in risk of dementia (Sabia et al., 2018).

In terms of CVDs, excessive alcohol consumption (>60 g/day in men and >40 g/day in women) (Fernández-Solà, 2015) is a well-known contributor to burden of CVDs (Di Castelnuovo et al., 2006; Gunzerath et al., 2004). In contrast, many observational studies have reported a “J-shaped” risk profile in which low to moderate alcohol consumption (≤ 60 g/day in men and ≤ 40 g/day in women) results in lower CVD risk compared to abstinence and excessive drinking (GBD 2016 Alcohol Collaborators, 2018; Ronksley et al., 2011). Whether this effect is truly causal or result from bias inherent to observational study designs remains unanswered. Overall, excessive alcohol consumption is one leading cause of general disability globally. In 2016, the harmful use of alcohol resulted in an estimated 3 million deaths (5.3% of all deaths) globally (World Health Organization, 2018). Despite the U-shape relationship between alcohol consumption and risk of dementia, it is not possible to assume that a light to moderate drinking of alcohol is protective toward dementia and/or cognitive decline. In 2019, WHO guidelines concluded that a general recommendation of alcohol consumption is not advisable, considering other health risks and the social and economic burden associated with alcohol (World Health Organization, 2019).

2.5 Risk factors related to dementia

2.5.1 Genetic and family history

In terms of heritability, a strong genetic link is more common in rarer types and early-onset dementia (<60 years), but these comprise only a minor proportion of overall cases. Three single-gene mutations associated with early-onset AD is known; amyloid precursor protein (*APP*) on chromosome 21 (Goate et al., 1991), presenilin 1 (*PSEN1*) on chromosome 14 (Sherrington et al., 1995), and presenilin 2 (*PSEN2*) on chromosome 1 (Levy-Lahad et al., 1995; Rogaev et al., 1995). Mutations in these genes cause nearly always predominantly inherited AD, but mutations in these genes represent less than 5% of AD cases (Guerreiro et al., 2012; Karch et al., 2014; Karch & Goate, 2015). In addition, several genes that increase the risk of AD have been found, but the significance of these is diminutive (Tanzi, 2012).

The strongest genetic impact on risk of late-onset AD is related to apolipoprotein E (*APOE*) gene. During 1993, several research groups around the world reported a clear link between polymorphism in the *APOE* gene on chromosome 19 and AD (Corder et al., 1993; Kuusisto et al., 1994; Noguchi et al., 1993; Poirier et al., 1993; Schmechel et al., 1993). Major alleles of *APOE* are called $\varepsilon2$, $\varepsilon3$ ja $\varepsilon4$, and combinations of these subtypes result in six phenotypes of *APOE*: $\varepsilon2/\varepsilon2$, $\varepsilon2/\varepsilon3$, $\varepsilon2/\varepsilon4$, $\varepsilon3/\varepsilon3$, $\varepsilon3/\varepsilon4$, and $\varepsilon4/\varepsilon4$ (Mahley, 1988). The proportion of these phenotypes varies between racial and ethnic groups (D. A. Evans et al., 2003; Rajan et al., 2017;

M. X. Tang et al., 1998). In both hereditary and sporadic AD, the e4 subtype is overrepresented in patients compared to the general population (Corder et al., 1993; Kuusisto et al., 1994; Noguchi et al., 1993; Poirier et al., 1993; Schmechel et al., 1993). At least one copy of the e4 allele of the *APOE* is found in 56% of AD cases, increasing risk 3-fold. Two copies are found in 11% of AD cases, increasing risk 8- to 12-fold (Holtzman et al., 2012; Loy et al., 2014; Ward et al., 2012). In addition, those with the $\varepsilon 4$ allele are more likely to have AD at a younger age than those with the $\varepsilon 2$ or $\varepsilon 3$ allele (Goedert et al., 1994; Spinney, 2014). It is possible that cognitive reserve modifies the risk of dementia attributable to *APOE*-$\varepsilon 4$. For example, in the Swedish Kungsholmen Project those with *APOE*-$\varepsilon 4$ had a decreased risk of developing dementia if they had more years of early life education, had mentally challenging work in midlife, participated in leisure activities in late life, and/or had strong social network in late life (Dekhtyar et al., 2019). People who have a first-degree relative with AD are more likely to develop the disease (Cannon-Albright et al., 2019; Green et al., 2002; Loy et al., 2014), and having more than one first-degree relative with AD increase the risk further (Cannon-Albright et al., 2019; Lautenschlager et al., 1996). Since 2009 to early 2022, the use of large genome-wide association studies has led to identification of nearly 100 risk loci related to late-onset AD (Kamboh, 2022).

Vascular dementia (VD) is not usually inherited, but certain genes that increase the risk of developing VD may be inherited. Often these same ones increase the risk of high blood pressure, diabetes, and stroke. Large number of studies have examined the contribution of genetic polymorphisms to the risk of sporadic VD, but the results have been conflicting. In 2015, a systematic review and meta-analysis highlighted the genetic contribution to sporadic VD. They concluded that strongest association was between *APOE* and VD (Sun et al., 2015). In addition, *APOE* increases the cerebral amyloid angiopathy, white matter hyperintensities, and hemorrhagic strokes (Biffi et al., 2010; Schilling et al., 2013). The genetic variation at the *APOE* may modify resilience of the brain when exposed to vascular risk factors (Zade et al., 2010). In the Framingham Study (Peloso et al., 2020), in the Rotterdam study (MahmoudianDehkordi et al., 2019), and in the UK Biobank study (Rutten-Jacobs et al., 2018), *APOE* and lifestyle factors had an additive impact on cognitive function and risk of dementia.

2.5.2 Depression

Depressive symptoms are common in patients with dementia and depression is part of the prodromal and early stages of dementia. Whether depressive symptoms and depression in adulthood is a truly modifiable risk factor for dementia or a marker of incipient dementia is still unsure and reverse causation is possible. The World

Alzheimer Report 2014 identified 32 studies concerning depression and dementia risk, with more than 62,000 participants, and follow-up from 2 to 17 years. They found a depressive episode was a risk factor for all-cause dementia (pooled effect size 2.0, 95% CI 1.7 to 2.3) (Prince et al., 2014). Consistently, a systematic review of six longitudinal meta-analyses found a significant association between depression and AD (OR=1.54, 95% CI 1.02 to 2.31; p=0.038) (Sáiz-Vázquez et al., 2021) and several other studies have concluded that late-life depression is related to an increased risk for all-cause dementia, VD, and AD (Diniz et al., 2013; Kuring et al., 2020).

On the other hand, the UK Whitehall II cohort study did not find increased risk for dementia even when chronic/recurring depressive symptoms occurred in midlife (Singh-Manoux et al., 2017). In late life, these symptoms increased dementia risk in 11 years follow-up (HR 1.7, 95%CI 1.2 to 1.4), but not in 22 years follow-up (1.0, 0.7 to 1.4) (Singh-Manoux et al., 2017). A 14-year longitudinal study of 4,922 cognitively healthy men aged 71–89 years observed a similar result. Depression was associated with a 1.5-fold (95% CI 1.2 to 2.0) incidence of dementia but this association was only apparent during the first five years of follow-up (Almeida et al., 2017). In the same study, the use of antidepressants did not decrease the risk of dementia.

The potential effect of antidepressant treatment in preventing dementia is still uncertain. In animal models, research has suggested that selective serotonin reuptake inhibitors (SSRIs) may reduce amyloid plaque burden and cognitive impairment (Cirrito et al., 2011; Fisher et al., 2016; Shen et al., 2011). In cognitively healthy individuals with depression, long-term treatment with SSRIs has been found to be associated with lower amyloid plaque load (Cirrito et al., 2011). An observational study of 755 people aged between 55 and 90 years, with MCI, and with a history of depression, evaluated the impact of SSRI treatment on progression from MCI to AD’s dementia. They found that long-term (>4 years) SSRI treatment was significantly associated with a delayed progression to AD’s dementia by approximately 3 years, compared with short-term SSRI treatment, no treatment, or treatment with other antidepressants (Bartels et al., 2018). Nevertheless, cerebrospinal fluid levels of amyloid-$ß_{1-42}$, tau, and p-tau did not differ between MCI patients with and without a history of depression (Bartels et al., 2018).

2.5.3 Infrequent social contact and loneliness

The hypothesis that social isolation accelerates cognitive decline in aging have been examined for decades (Berkman et al., 2000; Salthouse, 1991). Already in 2004, a systematic review concluded that an active and socially integrated lifestyle in late life protects against dementia and AD (Fratiglioni et al., 2004). Subsequently several studies have suggested that less social engagement increases the risk of cognitive decline (I. E. M. Evans et al., 2019; Kelly et al., 2017; Sommerlad et al., 2019). However, the range of indicators to assess social networks and social activity is wide and therefore the heterogeneity across studies has been broad (I. E. M. Evans et al., 2019). In addition, there is a risk of bias arising from reverse causality when social isolation prior to diagnosis of cognitive decline or dementia may be a part of the dementia prodrome (Livingston et al., 2020; World Health Organization, 2019).

Being married is associated with reduced risk of dementia. A systematic review and meta-analysis including 15 studies and over 800,000 participants worldwide found elevated dementia risk in lifelong single (RR=1.4; 95% CI 1.1 to 1.9) and widowed (1.2; 1.0 to 1.4) compared to married individuals (Sommerlad et al., 2018). In divorced people, they found no association.

Feelings of loneliness have been associated with MCI and increased risk of dementia (Kuiper et al., 2015; Lara, Caballero, et al., 2019; Lara, Martín-María, et al., 2019; Salinas et al., 2022), but the significance of this association is still unclear. In 2019, a systematic review and meta-analysis of longitudinal studies involving 37,339 individuals aged 64.9–83.1 years found loneliness was associated with increased risk of dementia (overall RR 1.26; 95% CI 1.14 to 1.40) (Lara, Martín-María, et al., 2019). Conversely, in the prospective UK Biobank study with 155,070 participants (mean age 64.1 years and mean follow-up 8.8 years) social isolation, but not loneliness, was associated with increased risk of dementia (HR 1.62, 95% CI 1.38 to 1.90) (Elovainio et al., 2022).

2.5.4 Hearing impairment

In the 2010s, hearing loss was considered a highly relevant modifiable risk factor for dementia (Livingston et al., 2017). By eliminating the hearing impairment, the risk of dementia could be reduced by 9% (Livingston et al., 2017). According to current evidence, the risk of dementia is higher in patients with hearing loss compared to healthy controls (Lin et al., 2013; Loughrey et al., 2018; Ralli et al., 2019; Y. Zheng et al., 2017).

Accelerated brain changes and reduced volume of auditory cortex are present in older adults with age-related hearing loss (Golub, 2017; Lin et al., 2014). Association between midlife hearing impairment measured by audiometry and steeper temporal lobe volume loss has been found (Armstrong et al., 2019).

The treatment of hearing loss may be an effective way to maintain cognition (Amieva et al., 2018; Lin et al., 2023), and the long follow-up prospective studies suggest that the use of a hearing aid is protective (Amieva et al., 2018; Maharani et al., 2018; Ray et al., 2018). Use of hearing aids in people with cognitive impairment may improve communication, increase quality of life, and reduce behavioral symptoms of dementia (Lin et al., 2011).

2.5.5 Traumatic brain injury

Traumatic brain injury (TBI) is usually caused by traffic accidents, sport injuries, falls, military exposures, and firearms (Bruns & Hauser, 2003), and is classified as mild, moderate or severe. The classification of TBI severity is based on duration and/or severity of symptoms, such as loss of consciousness, a loss of memory for events occurring before or after the injury, Glasgow Coma Scale, and alteration in mental status (e.g., confusion, dizziness, blurred vision, focal neurological symptoms, headache, and nausea) (Malec et al., 2007; Management of Concussion/mTBI Working Group, 2009). Due to a methodological challenge in classification, research on TBI as a risk factor for long-term brain changes and cognitive decline is limited (LoBue et al., 2019). However, a review from 2019 identified dozens of high-quality studies regarding of structural brain changes post-TBI, relation between TBI and accumulation of neurobiological markers related to neurodegenerative disease processes, and TBI-related risk for all-cause dementia, AD, frontotemporal dementia, and Lewy body disease (LoBue et al., 2019).

A more severe TBI was already in 1990s identified as risk factor for AD (Fleminger et al., 2003; Mortimer et al., 1991). Recent systematic reviews have found that TBI of any severity is associated with a 63%–96% increased risk of all-cause dementia (Huang et al., 2018; Y. Li et al., 2017; Snowden et al., 2020). For example, in a nationwide Danish cohort study of nearly 3 million people aged at least 50 years was followed for a mean of 10 years. An increased all-cause dementia (HR 1.2, 95% CI 1.2 to 1.3) and AD risk (1.2, 1.1 to 1.2) were found (Fann et al., 2018). Additionally, the all-cause dementia risk increased with number of TBI (one TBI 1.2, 1.2 to 1.3; ≥ 5 TBIs 2.8, 2.1 to 3.8) (Fann et al., 2018). In a Swedish cohort study of over 3 million people aged 50 years and older, the 1-year dementia risk after TBI was elevated (OR 3.5, 95% CI 3.2 to 3.8) and risk remained elevated over 30 years (1.3, 1.1 to 1.4) (Nordström & Nordström, 2018).

Chronic traumatic encephalopathy (CTE) is a neurodegenerative tauopathy linked to repetitive mild TBI and repetitive sub-concussive head trauma. CTE was first described in boxers, but subsequently in a variety of contact sport athletes, military veterans, and civilians exposed to repetitive mild TBI. Whether CTE is a risk factor for dementia is not yet established (D. H. Smith et al., 2019).

2.5.6 Other risk factors for dementia

In addition to the generally acknowledged risk factors to date, other factors have been associated with an increased risk of dementia in individual studies. These include for example, obstructive sleep apnea, sleep disorder, infections, inflammation, and air pollution.

Treatment of obstructive sleep apnea (OSA) may reduce the risk of subsequent dementia. In a retrospective study with over 53,300 adults with OSA, aged 65 and older, and follow-up three years, the positive airway pressure therapy was independently associated with lower odds of incident AD and dementia not otherwise specified (OR=0.78, 95% CI 0.69 to 0.89; OR=0.69, 95% CI 0.55 to 0.85) (Dunietz et al., 2021). Sleep disturbance is hypothesized to increase inflammation, which raises ß-amyloid burden leading to AD (Irwin & Vitiello, 2019). In 2020, a systematic review and meta-analysis identified six types of sleep conditions, which were linked to higher risk of all-cause cognitive disorders (W. Xu et al., 2020). In addition, there was a U-shaped relationship between sleep duration and cognitive disorders or AD. Altogether, mechanisms by which sleep might affect dementia are still unclear (Livingston et al., 2020).

Associations between infections and risk of dementia have been found in several independent cohorts (Mawanda et al., 2016; Muzambi et al., 2020; Shah et al., 2013; Tate et al., 2014), but it is still unclear whether certain infections, specific microbes, or general inflammation is the main cause of the increased risk. In a large, multicohort, observational study, severe infections requiring hospital treatment were associated with long-term increased risk of dementia (Sipilä et al., 2021). Their findings also support the hypothesis that general inflammation rather than specific microbes drive increased dementia risk (Sipilä et al., 2021). In prospective studies, systemic inflammation has been associated with accelerated cognitive decline and dementia (Darweesh et al., 2018; Iwashyna et al., 2010; Walker, Gottesman, et al., 2019).

Air pollution might act via vascular mechanism in the same way as smoking (Peters et al., 2019). A systematic review including 13 longitudinal studies with 1–15 years follow-up found exposure to fine ambient particulate matter, nitrogen dioxide, and carbon monoxide were all associated with increased risk of dementia (Peters et al., 2019).

2.6 Dementia risk indices

Dementia risk indices are tools that quickly and efficiently combine information on known risk factors of dementia. The main target is to identify individuals with a risk for dementia who can be referred for more frequent monitoring and early interventions to prevent or delay onset of cognitive decline (Barnes & Yaffe, 2011).

In addition, prognostic models can aid selection of high-risk individuals for clinical trials (Licher et al., 2018, 2019; Solomon & Soininen, 2015; Vonk et al., 2021). In the 2000s and 2010s, research in the field of dementia risk prediction has widely expanded. Already in 2010, a systematic review identified more than 50 different dementia risk prediction models, but only few of these were externally validated (Stephan et al., 2010).

Numerous models have been developed to be used for different focus groups. Risk scores for primary prevention of dementia are usually intended for middle-aged adults, since they highlight modifiable risk factors that are significant in middle age, and they predict risk of dementia later in life [e.g., CAIDE (Kivipelto et al., 2006)]. Risk scores for secondary prevention instead are targeted to individuals who already have symptoms of cognitive impairment. Cognitive decline may start 3–7 years prior to MCI and 10 years before the onset of dementia (Karr et al., 2018). Risk scores used in secondary prevention generally assess the risk of dementia over a few years, not over decades. Individuals may also have a chronic disease with an increased risk of dementia (Anstey et al., 2021). For example, dementia risk scores for populations with diabetes already exist (Exalto et al., 2013; C.-I. Li et al., 2018; H. B. Mehta et al., 2016).

Traditionally age, gender, family history of dementia, and genetics are considered as non-modifiable risk factors for dementia. They may interact with modifiable risk factors, but it is not obvious should or should they not be included in risk scores. However, non-modifiable risk factors may provide information for tailoring of interventions to individuals, planning risk reduction strategies, and guide allocation of resources at the population level (Anstey et al., 2021). In addition, understanding how modifiable and non-modifiable risk factors interact may motivate individuals to favor brain-healthy behavior. In terms of practicability and economics, dementia risk scores can be divided into those used in clinical settings and research environments. For example, polygenic risk scores (Najar et al., 2021; Stocker et al., 2021), *APOE*-e4 genotype, neuroimaging, and carotid artery ultrasound (Barnes et al., 2009) may improve the prediction of risk scores but are not widely available and may be costly. Thus, these kind of risk scores are more often used in research settings. Instead, risk scores that do not require expensive examinations or measurements are more suitable for primary health care.

Dementia risk models can be divided into the following categories: 1) models containing only demographic characteristics; 2) models based on cognitive test with or without subjective cognitive symptoms or demographic data; 3) models based on health variables and health risk indices (either self-reported or objectively measured health status); 4) genetic risk scores (genes alone or in combination with non-genetic variables); and 5) multi-variable models incorporating demographic, health and lifestyle measures (E. Y. Tang et al., 2015). The number of variables used for risk score varies from one (Ehreke et al., 2011) to 19 (Song et al., 2011) and the length of follow-up from 1.4 years (Ehreke et al., 2011) to 20 years (Kivipelto et al., 2006). Disease outcome is usually all-cause dementia, AD, or conversion of mild cognitive impairment to dementia.

2.6.1 Midlife dementia risk scores

The Cardiovascular Risk Factors, Aging and Dementia (CAIDE)

The CAIDE risk score uses risk factors in midlife to estimate an individual's risk of later life dementia. The model was developed in a sample of 1,409 Finns aged 39 to 64 years with mean follow-up of 20 years. The midlife risk factors incorporate age, education, gender, blood pressure, body mass index, total cholesterol, and physical activity (Kivipelto et al., 2006). In external validation with Kaiser Permanente cohort (*n*=9,480; age range 40 to 55 years; mean follow-up 36.1 years), similar moderate predictive accuracy was reported between the original cohort and validation cohort, but also when stratified by ethnicity (original cohort AUC=0.78, validation cohort AUC=0.75, Asian AUC=0.81, Black AUC=0.75 and White AUC=0.74). During the external validation, the study attempted to improve the discriminative accuracy of the CAIDE score with the addition of new variables. Nevertheless, significant improvement was not found when risk factors such as central obesity, depressed mood, diabetes, head trauma, poor lung function and smoking were tested (Exalto, Quesenberry, et al., 2014).

In older aged cohorts, the CAIDE risk score has been poor in predicting dementia. In external validation with the Rush Memory and Aging Study (*n*=903, age ≥53 years), the Kungsholmen Project (*n*=905, age ≥75 years), and the Cardiovascular Health Cognition Study (*n*=2,496, age ≥65 years) AUC for all-cause dementia and AD range from 0.49 to 0.57 (Anstey et al., 2014). When BMI or BMI and cholesterol level together were excluded, the discriminative accuracy was slightly better: 0.55 to 0.60 for all-cause dementia and 0.55 to 0.58 for AD (Anstey et al., 2014).

The education and occupation-based middle age self-report risk score

The middle age self-report risk score was the first entirely education and occupation-based risk score that predicts the risk of cognitive impairment in old age (Vuoksimaa et al., 2016). The score is based on a longitudinal population-based Finnish Twin Cohort study, where all participants were Finnish twins from same-sex pairs born before 1958. At a mean age of 47 years, cognitive reserve was determined by education, work status, nature of work, work environment and the physicality of work. After a mean follow-up of 28 years (at a mean age of 74 years), the cognitive status was determined via two validated telephone instruments. The risk score was significantly associated with cognition and dementia in old age. The AUC for this model was 0.77. In subsequent twin-pair analyses, the score gave little support for associations independent of shared environmental and genetic factors (Iso-Markku et al., 2021).

The Clinical Risk Score Prediction Tool

The Clinical Risk Score Prediction Tool is based on a large prospective UK population-based cohort study conducted in 2006–2010 (Ren et al., 2022). A total of 444,695 participants [205,187 men; mean (SD) age, 56.7 (8.2) years; 239,508 women; mean (SD) age, 56.2 (8.0) years] were originally dementia free. During the 13-year follow-up dementia occurrence was 0.7% for men and 0.5% for women. According to this study, men and women shared some modifiable risk and protective factors (e.g., sleepiness, underweight, and low frequency of alcohol use) but they also presented independent risk factors (e.g., employment status and educational level). Altogether, these factors accounted for 32% of men developing dementia and 53% of women developing dementia. The prediction tool included 16 characteristics: demographic (age, educational level, body mass index and employment status), lifestyle factors (smoking and frequency of alcohol consumption), sleep phenotype (early awakening, sleepiness, insomnia, and snore), and comorbidities (respiratory disease, cancer, cerebrovascular disease, diabetes, CVD, and hypertension). The predictive accuracy for 13-year dementia risk was high, almost 100%, but this prediction tool is not yet externally validated.

The Lifestyle for Brain Health (LIBRA)

The LIBRA risk tool is based on risk factors selected from a review of the literature and a Delphi consensus study (Deckers et al., 2015). At the baseline, the LIBRA score was calculated for 949 participants aged 50–81 years from the Maastricht Ageing Study (Schiepers et al., 2018). The observation period was up to 16 years. The tool includes only modifiable risk factors: hypertension, hypercholesterolemia, obesity, physical inactivity, diabetes, depression, smoking, alcohol consumption, cognitive activity, healthy diet, coronary heart disease, and renal dysfunction. In a study of 9,387 individuals having no dementia recruited from the European population-based DESCRIPA study, the LIBRA index predicted dementia (Vos et al., 2017) at midlife (55–69 years old) and in late-life (70–79 years old). In the 80–97 age group higher LIBRA scores did not increase the risk for dementia (Vos et al., 2017).

The predictive accuracy of the LIBRA has also been examined with the Finnish CAIDE population. The score was calculated for CAIDE participants in midlife (*n*=1,024) and twice in late life (*n*=604) up to 30 years later (Deckers et al., 2020). Higher midlife LIBRA scores were related to higher risk of dementia (HR=1.27; 95% CI 1.13 to 1.43) and MCI (1.12; 1.03 to 1.22). Instead, higher late-life LIBRA scores were related to higher risk of MCI (1.11; 1.00 to 1.25), but not dementia (1.02; 0.84 to 1.24).

2.6.2 Late-life dementia risk models for primary care

The Dementia Screening Indicator (DSI)

The DSI was developed for predicting 6-year incident dementia among people aged 65–79 years specifically in primary care (Barnes et al., 2014). Data synthesis was based on the best dementia predictors identified in four different cohort studies: The Cardiovascular Health Study (CHS) (Fried et al., 1991), the Framingham Heart Study (FHS) (Dawber & Kannel, 1966), the Health and Retirement Study (HRS) (National Institute on Aging, 2007), and the Sacramento Area Latino Study on Aging (SALSA) (Haan et al., 2003). Potential predictive factors available in most or all cohorts were identified, and then in each cohort, most predictive variables at six years were identified independently. The final DSI included variables that were found consistently in all four cohorts: age, education, history of stroke, diabetes mellitus, BMI, depressive symptoms, and requiring assistance with money or medications. Accuracy was good across the cohorts and different race/ethnic groups. The c-statistic was 0.68 in CHS (0.70 Whites, 0.65 Blacks), 0.77 in FHS, 0.76 in HRS (0.75 Whites, 0.70 Blacks, 0.71 Latinos), and 0.78 in SALSA. Participants identified as high risk based on the DSI ranged from 6% in FHS to 27% in SALSA.

The Late Life Dementia Risk Index (LDRI) and the Brief Dementia Risk Index (BDRI)

The LDRI was developed to stratify older adults (≥65 years) into those with low, moderate, or high risk of developing dementia within six years (Barnes et al., 2009). Data were derived from the Cardiovascular Health Cognition Study with 3,375 participants without evidence of dementia and mean age of 75 years at baseline. The original intensive model included demographic (age), lifestyle (alcohol consumption), neuropsychological (Modified Mini Mental State Examination score and Digit Symbol Substitution Score), medical (history of coronary bypass surgery and BMI), physical functioning (time to put on and button a shirt in seconds), genetic (*APOE*), cerebral magnetic resonance imaging (white matter disease and enlarged ventricles), and carotid artery ultrasound (internal carotid artery thickness >2.2 mm) measures. The LDRI had good discrimination for the prediction of 6-year incident dementia (c-statistic = 0.81; 95% CI 0.79 to 0.83), but it includes measures that would be impractical to perform in most clinical settings due to time, feasibility, and cost. The BDRI is an abbreviated version from LDRI, and it can be used both in clinical and research settings to identify high-risk individuals (Barnes et al., 2010). The BDRI, including a combination of age and cognitive, lifestyle and cardiovascular factors, is validated among older (≥65 years) population (Barnes et al., 2010).

The Australian National University Alzheimer's Disease Risk Index (ANU-ADRI)

The ANU-ADRI was developed using an evidence-based medicine approach to assess a persons' risk for later life AD (i.e., over 60 years of age) (Anstey et al., 2013, 2014). There was no development dataset. Rather, the model was tested in three different cohorts: The Rush Memory and Aging Study (MAP) (n=903, age ≥53 years), the Kungsholmen Project (KP) (n=905, age ≥75 years), and the Cardiovascular Health Cognition Study (CHCS) (n=2,496, age ≥65 years). The index is based on eleven risk and four protective factors that are associated with Alzheimer's disease. Risk factors include age, sex, education, body mass index, diabetes, depressive symptoms, serum cholesterol, traumatic brain injury, smoking, low social network and engagement, and occupational pesticide exposure. Protective factors include alcohol consumption, cognitive activity, physical activity, and fish intake. In external validation, MAP had ten, KP eight and CHCS nine of these 15 factors. The predictive accuracy of ANU-ADRI was moderate in all three cohorts. The AUC for all-cause dementia in MAP was 0.72 and for AD 0.73, in KP 0.65 and 0.64, and in CHCS 0.73 and 0.74, respectively.

Prediction of dementia in primary care patients based on AgeCoDe -study

The risk score for primary care patients is based on the German Study on Aging, Cognition and Dementia (AgeCoDe) (Jessen et al., 2011). In this longitudinal cohort study of 3,055 individuals having no dementia above 75 years, three follow-up investigations were performed at 18 months intervals. The primary outcome was all-cause dementia. The score comprises age, subjective memory impairment, performance on delayed verbal recall and verbal fluency, Mini Mental State Examination, and instrumental activities of daily living. A prediction accuracy for AD in the development cohort was 0.84 and in the test cohort 0.79.

The Type-2 Diabetes Specific Dementia Risk Score (DSDRS)

The DSDRS was developed in a primary care setting for predicting 10-year incident dementia among people aged 60 years and older with type 2 diabetes (Exalto et al., 2013). The score includes age, education, microvascular disease, diabetic foot, cerebrovascular and cardiovascular disease, acute metabolic event, and depression. The DSDRS is well calibrated and externally validated. The predictive accuracy was moderate in both the development cohort (AUC=0.74) and in the validation cohort (AUC=0.75.

Risk factors incorporated in the midlife and in the late-life dementia risk scores are presented in tables 5 and 6.

Table 5. Risk factors in midlife dementia risk scores.

Risk factor	CAIDE	The Clinical Risk Score Prediction Tool	LIBRA
Age	x	x	
Education	x	x	
Gender	x		
Blood pressure	x	x	x
BMI	x	x	x
Cholesterol	x		x
Smoking		x	x
Alcohol consumption		x	x
Physical activity	x		x
Cognitive activity			x
Employment status		x	
Healthy diet			x
Sleep phenotype		x	
Respiratory disease		x	
Cancer		x	
CVD		x	CHD
Cerebrovascular disease		x	
Diabetes		x	x
Depression/ depressive symptoms			x
Renal dysfunction			x

Table 6. Risk factors in late-life dementia risk scores.

Risk factor	DSI	BDRI	ANU-ADRI	AgeCoDe	DSDRS
Age	x	x	x	x	x
Education	x		x		x
Gender			x		
BMI	x	x	x		
Cholesterol			x		
Smoking			x		
Alcohol consumption		x	x		
Physical activity			x		
Cognitive activity			x		
Fish intake			x		
CVD					x
Coronary artery bypass surgery		x			
Peripheral artery disease		x			
Cerebrovascular disease	x	x			x
Diabetes	x		x		
Diabetic foot					x
Microvascular disease					x
Depression/ depressive symptoms	x		x		x
Traumatic brain injury			x		
Acute metabolic event					x
Requiring assistance with money or medication	x				
IADL				x	
MMSE				x	
Delayed recall		x		x	
Verbal fluency				x	
Incorrectly copying intersecting pentagons		x			
Incorrectly taking or folding a paper		x			
Inability to name 10 four-legged animals in 30 sec		x			
Subjective memory impairment		x		x	
Low social network			x		
Occupational pesticide exposure			x		

2.7 Multidomain interventions to prevent cognitive decline and Alzheimer's disease

There is evidence that targeting multiple modifiable risk factors (MRFs) simultaneously is more effective than targeting single MRF in the prevention of cognitive decline and AD (Kivipelto et al., 2020). A review up to May 2021 identified nine studies on the effect of multidomain lifestyle interventions on cognition and/or AD incidence or risk scores (Noach et al., 2023). These studies were all RCTs, and they included a combination of separate intervention components; diet, physical activity, cognitive activity, metabolic or CV risk factor reduction strategies, social activity, medication, and/or supplementation (Andrieu et al., 2017; L.-K. Chen et al., 2020; Clare et al., 2015; de Souto Barreto et al., 2021; Moll van Charante et al., 2016; Ngandu et al., 2015; Richard et al., 2019; Williamson et al., 2019; Z. Xu et al., 2020). The review observed no effect on AD incidence, but positive results were shown for AD risk scores. Additionally, significant effects of multidomain lifestyle intervention studies on global cognition were found (Andrieu et al., 2017; L.-K. Chen et al., 2020; Ngandu et al., 2015; Z. Xu et al., 2020), and significant improvements in cognition for specific cognitive domains (L.-K. Chen et al., 2020; Ngandu et al., 2015). Overall, multidomain lifestyle interventions may be partially effective in preventing cognitive decline, but it is still unclear whether multidomain interventions can prevent AD.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER) was the first multidomain lifestyle intervention to show that targeting to multiple MRFs is beneficial for prevention of cognitive decline (Ngandu et al., 2015). In the FINGER study, 1,260 Finnish older adults aged 60–77 years (mean age 69.4 years) according to CAIDE at risk of dementia were randomized (1:1) into intervention and control groups. The intervention group received dietary guidance (according to national recommendations), physical activity, cognitive training, social activities, and metabolic and vascular risk factor management. The control group received general health advice. The active intervention period lasted for two years. Since that, participants have been followed up by control visits five, seven, and eleven years after the end of the intervention (Finnish Institute for Health and Welfare, 2023).

The intervention improved global cognition measured by neuropsychological test battery (NTB) Z score, executive functioning, and processing speed compared to control. In addition, the intervention reduced the risk of cognitive decline. The intervention was beneficial regardless of genetic risk or baseline risk factor levels

(Solomon et al., 2018). In the intervention group, health related quality of life and physical functioning were better maintained, and there were less new chronic diseases (Kulmala et al., 2019; Strandberg et al., 2017). Based on FINGER study, the Finnish institute for health and welfare has launched a model to support implementation of the study results in everyday practice. The model includes identification of those at risk of cognitive decline, and advice on how to promote healthy lifestyles supporting healthy aging in health care. Globally, the World Wide FINGERS network has been launched to plan and conduct FINGER like trials worldwide (Kivipelto et al., 2020).

The Multidomain Alzheimer Preventive Trial

The multidomain Alzheimer preventive trial (MAPT) was a 3-year, multicenter, randomized trial carried out in France and Monaco (Andrieu et al., 2017). Participants were 1,525 people having no dementia, community-dwelling, and aged 70 years or older (mean age 75.3 years). They had either relayed a spontaneous memory complaint to their physician, limitations on one instrumental activity of daily living, or slow gait speed. The intervention components were same as in the FINGER study, except for social activities and the addition of the dietary supplement omega-3 polyunsaturated fatty acids (PUFAs). Participants were randomized (1:1:1:1) to 1) multidomain intervention plus omega-3 PUFAs, 2) multidomain intervention plus placebo, 3) omega-3 PUFAs alone, or 4) placebo alone. Effects on global cognition were similar to the FINGER study as the multidomain intervention groups had less cognitive decline. However, statistical significance was only reached in post-hoc analysis of pooled multidomain intervention.

Prevention of dementia by intensive vascular care

The Dutch study Prevention of dementia by intensive vascular care (PreDIVA) evaluated whether a multidomain intervention targeting to CV risk factors can prevent dementia in a general population of community-dwelling older adults (Moll van Charante et al., 2016). Participants (n=3,526) were aged 70–78 years (mean age 74.5 years), and they were randomized 1:1 to either a 6-year nurse-led, multidomain CV intervention or control. The intervention included physical activity, management of CV risk factors (e.g., targeting healthy BMI, diet, no smoking, low cholesterol, and normal blood pressure), and medical interventions when needed. The intervention had no effect on incidence of all-cause dementia, incidence of AD, disability, incidence of CVD, or cognitive decline compared to control after a median follow-up 6.7 years.

Healthy ageing through internet counselling in the elderly

The healthy ageing through internet counselling in the elderly (HATICE) trial was carried out in the Netherlands, Finland, and France (Richard et al., 2019). Participants were 2,724 community-dwelling older adults, aged 65 years or over (mean age 69 years), and at increased risk of CVD. The trial aimed to determine whether a coach-supported internet intervention for self-management could reduce CV risk. Intervention contained diet, physical activity, and CV risk factor management. Participants were randomized 1:1 to either 18-month interactive supportive web-based intervention or to control group with a static online information platform. The intervention did not have any effect on the measured cognitive outcomes, but it decreased the risk of dementia and the intervention group improved in systolic blood pressure, BMI, and LDL-cholesterol compared to control group.

The Taiwan Multidomain Intervention Efficacy Study

In the Taiwan multidomain intervention efficacy study 1,082 prefrail/frail community-dwelling older adults aged 65 years and over (mean age 75.1 years) with subjective memory complaints and /or loss of at least one IADL, and/or slow gait speed were randomized to multidomain intervention group and to usual health education group as control (L.-K. Chen et al., 2020). The intervention included nutrition and disease education, physical activity, and cognitive training, and lasted 12 months. The intervention significantly improved concentration and resulted in higher general cognitive performance compared to control. Among the participants aged 75 years and over, the improvement on cognition was significant.

2.8 Benefits of defining dementia risk

Assessing the risk of dementia has many benefits at the individual and population level, as well in research and in the personalized medicine (Anstey et al., 2021). At the individual level, considering the dementia risk both in middle-age and in old-age 1) helps to identify individuals at the high risk, 2) make it possible to target risk reduction strategies, and 3) provide patients a goal to work toward and thus motivate those at high risk to improve their health behaviors. For example, the CAIDE risk score is suitable to use, and it should be used already in midlife in occupational health care. When using risk scores repeatedly, for example in annual health checks, it is possible to monitor the effectiveness of preventive activities (Curran et al., 2021). In late-life, dementia risk scores help to identify those who benefit from closer monitoring e.g., in senior health clinics. If cognitive decline then progresses, it is possible to initiate cognitive rehabilitation as early as possible. The main target is to delay decline in functional capacity and maintain independent living, which are essential as the Finnish old age policy emphasizes priority of living at home (Ministry of Social Affairs and Health, 2020).

At the population level, risk scores can be used to analyze and evaluate population health over time (Hamad et al., 2015). Based on this data, it could be possible to identify geographical areas with high number of individuals with elevated risk for dementia (Bagheri et al., 2018). Furthermore, data from risk scores could guide the allocation of resources in healthcare.

Even though disease-modifying drugs are not yet widely available (Cummings, 2023; Jönsson et al., 2023), multidomain life-style interventions may delay the onset of dementia (Ngandu et al., 2015). The challenge is to detect high-risk individuals to whom these interventions should be targeted. In a research context, risk scores help to select individuals for clinical trials (Ngandu et al., 2015), design interventions targeted for specific risk profiles, measure the impact of interventions on dementia risk in real time, and track trends and changes in dementia risk profiles over time (Solomon et al., 2019). When dementia risk score is further developed into risk tool, it can be converted into apps and websites [e.g., (Sindi *et al.*, 2015; *Online Dementia Risk Assessment*)]. These tools can then be used in personalized medicine services if they also include detailed biological and clinical information. In the most extended versions of risk tools, the use of biomarkers (e.g., genetic, blood, and brain markers) can lead to very specific risk assessments. The aim of precision medicine is to identify the most effective interventions accurately and efficiently for a specific patient. These kinds of tools offer tailored recommendations about non-pharmacological and pharmacological therapies (Behl et al., 2022; Reitz, 2016).

2.9 Factors predicting long-term care among older adults

Most older people want to live in their homes for as long as possible, and that is also in accordance with the Finnish old age policy. However, as people get older the need for long-term care in nursing homes and sheltered housing increases. Identification of predictive factors on long-term care among older people is of utmost importance to prevent and postpone long-term care.

Prediction models suitable for assessing the need for long-term care have been developed since the 1980s (Branch & Jette, 1982). These models can help clinicians and policy makers to provide most appropriate care and health services for older patients. Many studies have examined predictors of nursing home placement in the older people (Luppa, Luck, Weyerer, et al., 2010), but in 2015, a systematic review identified only four risk-prediction instruments for community-dwelling older adults of which two were externally validated (O'Caoimh et al., 2015). Since then, new prediction indices have been developed based on clinical frailty scales, laboratory data, or a combination of these (Blodgett et al., 2016; Heikkilä et al., 2021, 2023; McClintock et al., 2018), and at least one has been externally validated (O'Caoimh, 2023). Despite the scarcity of risk scores for long-term care, the importance of single risk factors is well known.

Dementia and cognitive impairment are considered the most common risk factors for long-term care (Andel et al., 2007; Cepoiu-Martin et al., 2016; Gaugler et al., 2007; Gnjidic et al., 2012; Hajek et al., 2015; Luppa et al., 2008; Luppa, Luck, Weyerer, et al., 2010), the risk increasing up to 17-fold (Luppa, Luck, Weyerer, et al., 2010). In addition, multiple factors influence the need for long-term care: gender, difficulties in activities of daily living [i.e. grooming/personal hygiene, dressing, toileting/continence, transferring/ambulating, and eating (Mlinac & Feng, 2016)], and in instrumental activities of daily living [i.e. activities that allow an individual to live independently in a community (Guo & Sapra, 2022)], multimorbidity and several chronic conditions (depression and other mental health problems, Parkinson's disease, stroke, heart disease), susceptibility to falls, hearing impairment, social factors (living alone, widowhood, low amount of social interaction), self-rated health, frailty, walking ability, low body mass index, and use of domestic help (Aguero-Torres et al., 2001; Andel et al., 2007; Gnjidic et al., 2012; Hajek et al., 2015; Halonen et al., 2019; Koller et al., 2014; Kurichi et al., 2017; Luppa, Luck, Matschinger, et al., 2010; Luppa, Luck, Weyerer, et al., 2010; Luppa et al., 2012; McClintock et al., 2018; Nihtilä et al., 2008; Salminen et al., 2017; Viljanen et al., 2021a, 2021b).

3 Aims

The purpose of this thesis is to describe secular changes in cardiovascular risk profiles and dementia risk indices in two birth cohorts of 70-year-olds born 20 years apart. In addition, predictive factors of long-term care and the future need for long-term care among older Finnish people born in 1940 was predicted.

The specific aims of each study included in this thesis were:

1. To describe and compare cardiovascular morbidity and risk factor profiles and prevalence of statin use in two 70-year-old cohorts examined 20 years apart (Study I).
2. To compare dementia risk indices between two birth cohorts of 70-year-olds born 20 years apart (Study II).
3. To assess the association of the Brief Dementia Risk Index with incidence of dementia among community-dwelling 70-year-olds over a five-year follow-up (Study III).
4. To examine factors predicting long-term care in home-dwelling 70-year-olds (Study IV).
5. To predict the future need for long-term care among older Finnish people born in 1940 (Study V).

4 Materials and Methods

4.1 Study design and study populations

The sub-studies of this thesis are based on two prospective cohort studies, the Turku Elderly Study, and the New Turku Elderly Study. Both studies are designed to examine the determinants of successful aging.

The study populations consisted of two birth cohorts of community-dwelling citizens at the age of 70 and living in the city of Turku, in Southwest Finland [in 1990 population ca 159,000 inhabitants of which 16.2% aged 65 years and over, in 2010 population ca 177,000 inhabitants of which 18.1% aged 65 years and over (Statistics Finland, 2024)]. The cohorts studied were born 20 years apart, the first in 1920 (The Turku Elderly Study, Turun vanhustutkimus, TUVA) and the second in 1940 (The New Turku Elderly Study, Uusi Turun vanhustutkimus, UTUVA). The data on participants eligible for inclusion in both cohorts were obtained from the central population register.

The Turku Elderly Study (TUVA) was initiated in the beginning of 1990s, when all residents born in 1920 and living in the city of Turku were invited to the survey (*n*=1,503). Altogether 37 people had died before the first invitation was sent, resulting in 1,466 possible participants at the baseline. Of those, 147 declined, 264 did not answer or were institutionalized, and 23 withdrew later resulting 1,032 participants who completed the baseline studies (70% of those invited). In the Turku Elderly Study, baseline health examinations were carried out at health centers in 1991–1992 by experienced general practitioners and research nurses. The 1920 birth cohort was since followed-up for mortality and morbidity for 25 years. The follow-up studies conducted 10, 15, 20, and 25 years after the baseline examination by several geriatricians.

The 1940 birth cohort (*n*=1,344) were invited to participate in the New Turku Elderly Study (UTUVA) at the beginning of 2010s. Altogether 37 people had died, moved, or institutionalized before the first invitation was sent, resulting in 1,307 eligible participants at the baseline. Of them, 303 did not answer, 22 declined, and 22 withdrew later. A total of 960 (73% of those invited) participated in the study. In the New Turku Elderly Study, a resident of geriatric medicine and research nurse accomplished all the baseline physical examinations in the Turku City Hospital. The

1940 birth cohort has since been followed-up for mortality and morbidity for 10 years.

4.2 Data collection

4.2.1 Baseline data collection

Both cohorts underwent the same three-phase examination protocol at baseline. The data were collected by using postal questionnaires, interviews, and clinical examinations in 1991–1992 (The Turku Elderly Study) and 2011–2012 (The New Turku Elderly Study).

First, the participants filled up a posted questionnaire. They were asked about their social status, education and occupation, residence, functional capacity, and limitations, need for help in daily living, self-reported health and cognitive symptoms, hobbies, alcohol consumption, smoking habits, common symptoms, diagnosed diseases, use of medications, and need for different kind of aids (e.g., glasses and hearing aid).

Second, after returning the questionnaire, the study nurse met the participants. The laboratory tests were taken after a 12-hour overnight fast. Height, weight, waist circumference, and electrocardiogram (ECG) were measured, and cognitive tests were performed after breakfast or on a separate visit.

Third, the participants met the physician. They checked together the questionnaire and if necessary, completed it. The study physician had access to all previous data in the local patient information system, including laboratory and x-ray results. All previously diagnosed diseases and medications in use were confirmed.

Participants self-reported use of both prescribed and over-the-counter medications and vitamins. In the New Turku Elderly Study, the researcher had also access to each participant's medical records from the municipal health center including home care and the Turku University Hospital allowing her to verify prescribed medicines. Prescriptions from private health care were unverifiable. The list of regular and as-needed medication were based on each participant's actual self-reported use over the past two weeks rather than his or her prescribed use. Medications were classified according to the specific Anatomic Therapeutic Chemical (ATC) classification system (2010 revision).

4.2.2 Physical examination

In the physical examination, blood pressure was measured in lying, sitting, and standing. For Peak expiratory flow (PEF) determination, Mini-Wright Standard Range Peak Flow Meter was used. The handgrip strength was measured with the

Saehan hydraulic hand dynamometer. As a part of physical evaluation, the four-meter gait speed test was conducted. The visual acuity and sense of hearing were tested. Need for hearing aid and/or glasses were detected. Cardiovascular examination comprised auscultation of heart and lung sounds, palpation of peripheral pulses, and detection of edema and shortness of breath. The NYHA-class was defined according to classification of New York Heart Association (The Criteria Committee of the New York Heart Association, 1994). Neurological examination comprised speech fluency, Romberg's test, spasticity, rigidity, hypokinesia, passive tremor, symmetry of movements, test of biceps, triceps, patellar and Achilles tendon reflexes, finger to nose and heel to shin tests.

4.2.3 Laboratory tests

Laboratory tests included blood count, erythrocyte sedimentation rate, lipid values, fasting glucose, hemoglobin A1c, cobalamin, creatinine and thyreotropin. In addition, a sample for DNA isolation was taken.

4.2.4 Mental examination

In the Turku Elderly Study, depressive symptoms were assessed by using the Zung depression scale and in the New Turku Elderly Study by using both the Zung scale and the 15-item Geriatric Depression Scale (GDS-15).

The Zung Self-Rating Depression Scale is a 20-item self-report questionnaire (Zung, 1986). Each item is scored on a Likert scale ranging from 1 to 4. A total score is derived by summing the individual item scores and it range from 20 to 80. Originally, the prime focus was on 20- to 64-year-olds, but Zung has also reported cut-off score for those aged 65 and older (Zung, 1972). The Zung depression scale bas been externally validated (Biggs et al., 1978). In the New Turku Elderly Study, the GDS-15 was performed as an interview. The questions have a yes/no format to be easy to understand for older people who may suffer from impaired cognitive function. Total scores range from 0 to 15, a higher score indicates more depressive symptoms (Sheikh & Yesavage, 1986). GDS-15 has been shown to have acceptable internal consistency and reliability (i.e., Cronbach's $\alpha \geq 0.70$) in older adults in a range of populations (Friedman et al., 2005; Pomeroy et al., 2001). A systematic review of the criterion validity of the GDS-15 item version reported that using various cut points GDS-15 had a mean sensitivity of 0.805 and mean specificity of 0.750 (Wancata et al., 2006).

4.2.5 Cognitive tests

All cognitive tests were performed in Finnish or Swedish, depending on participant's native language. In both cohorts, the Mini Mental State Examination (MMSE) was used as a global cognitive measure, with maximum score of 30 and a minimum score of 0 corresponding to the highest and the lowest level of cognitive function (Folstein et al., 1975). In addition, in the New Turku Elderly Study, the Clinical Dementia Rating Scale and two sections of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) were performed.

The Clinical Dementia Rating Scale (CDR) is a global rating device to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias. These six domains are memory, orientation, judgment, and problem solving, community affairs, home and hobbies, and personal care. The CDR was first introduced in a prospective study of patients with mild "senile dementia of Alzheimer's type" in 1982 (C. P. Hughes et al., 1982). New and revised CDR scoring rules were later introduced (Berg, 1988; Morris, 1993, 1997). In the New Turku Elderly Study, the CDR was estimated based on a semi-structured interview of the participant and on the clinical judgment of the clinician. The CDR is based on a scale of 0–3: no cognitive impairment (CDR=0), possible mild cognitive impairment (CDR=0.5), mild cognitive impairment (CDR=1), moderate cognitive impairment (CDR=2), and severe cognitive impairment (CDR=3). Interrater reliability of CDR in a multicenter trial was moderate to high but showed limitations in detecting early dementia (Rockwood et al., 2000).

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was funded by the National Institute on Aging in 1986 to develop standardized, validated measures for the assessment of Alzheimer's disease (Morris et al., 1989). Nowadays CERAD is widely used and has been translated into several languages and validated within different cultural contexts (Fillenbaum et al., 2008). In the New Turku Elderly Study, two tests from CERAD battery were performed: wordlist learning test and wordlist delayed recall. In the wordlist learning test, a ten-item wordlist is presented over three trials at the rate of one every 2 seconds with a different word order in each trial. The number of words correctly recalled is calculated for each of the three learning trials. The maximum number of correct responses is 30 (i.e., 10 for each of the three trials), with higher numbers indicating better learning performance. In the wordlist delayed recall test, the previously learned ten-item wordlist is recalled after 5 minutes. The maximum score for delayed recall is 10. Wordlist delayed recall has proved out to be sensitive in detecting mild AD in different populations (Karrasch et al., 2005; Künig et al., 2006; J. H. Lee et al., 2002; Welsh et al., 1991).

4.3 Definition of variables in the Study I

The prevalence of cardiovascular diseases (CVDs), cardiovascular risk factors and use of medication in both cohorts were calculated and compared. The diagnoses were mainly based on previous diagnoses, but results of laboratory tests and clinical examinations were also considered. The total number of the following CVDs and risk factors were counted: coronary heart disease (CHD), peripheral artery disease (PAD), ischemic stroke/transient ischemic attack (TIA), diabetes mellitus (DM), hypertension, smoking, and dyslipidemia (LDL-c values ≥ 3 mmol/l). The diagnosis of CHD was based on previous diagnosis and in addition, pathologic q-waves in the current ECG and a history of typical exercise-induced angina pectoris were considered indicative of CHD. The diagnosis of PAD was based on previous diagnosis or vascular procedures. In addition, the signs of weakened blood flow in the lower extremities (cold, atrophic skin, no pulses palpable) together with a typical gait pain (claudication) were considered diagnostic as well. Repeatedly measured fasting glucose values of > 7 mmol/l were considered indicative of DM, and blood pressure (BP) of ≥ 160/90 mmHg was defined as hypertensive.

The use of any medication, statins (ATC code C10AA), antidiabetic medication (A10), antihypertensive medication, and cardiovascular medication was calculated for both cohorts. Cardiovascular medication included nitrates and cardiac glycosides (C01), miscellaneous cardiovascular drugs (C02), diuretics (C03), beta-adrenoceptor blockers (C07), calcium antagonists (C08), angiotensin-converting-enzyme inhibitors and angiotensin II-receptor blockers (C09). Antihypertensive medication included all the above-mentioned groups except nitrates and cardiac glycosides (C01).

Based on participants' estimated CVD event risk, they were classified into three mutually exclusive risk groups. Risk group classification was made regardless of statin use. Participants with known CVD (CHD, PAD, stroke/TIA) and/or DM comprised the high-risk group. Moderate-risk group consisted of participants free of CVD and DM, but who used cardiovascular medication. Those who did not have CVD, DM, or hypertension, and who did not use any cardiovascular medication (but may have used statins) were considered as low-risk group. In the 1940 cohort, the proportions of participants in the three risk groups were calculated stratified by statin use.

4.4 Dementia risk indices in the Study II

Dementia risk was assessed and compared between the 1920 and 1940 birth cohorts with the CAIDE Dementia Risk Score (*n*=1,516), the Brief Dementia Risk Index (*n*=1,598) and the Dementia Screening Indicator (*n*=1,462). Participants with missing data of dementia risk indices were excluded.

4.4.1 The CAIDE Dementia Risk Score

The CAIDE Dementia Risk Score is a seven-item risk index (range 0–15), which includes age, education, gender, blood pressure, body mass index, total cholesterol, and physical activity. In this study, physical inactivity was defined as not having daily outdoor activities. Otherwise, the risk score was used as original. Those scoring six or more points have shown to have an elevated risk for developing dementia during the following 20 years among Finnish middle aged (39–64 years) population (Kivipelto et al., 2006). The original CAIDE score also includes a cut-off of nine points. In this study, the cut-off of six points was chosen to make CAIDE and the Brief Dementia Risk index be more comparable in terms of moderate and high risk.

CAIDE Risk Score used in study II

Risk factor		Points
Age (years)	< 47	0
	47–53	3
	> 53	4
Education (years)	≥ 10	0
	7–9	2
	0–6	3
Gender	Female	0
	Male	1
Systolic blood pressure (mmHg)	≤ 140	0
	> 140	2
Body-mass index (kg/m^2)	≤ 30	0
	> 30	2
Total cholesterol (mmol/l)	≤ 6.5	0
	> 6.5	2
Physical activity	Active[a]	0
	Inactive (no daily outdoor activities)	1

[a] In the original CAIDE active is defined as at least twice a week, lasting at least 20-30 minutes each time, and causing sweating and breathlessness

4.4.2 The Brief Dementia Risk Index (BDRI)

The BDRI consists of 11 items (range 0–13): age, recall of three words presented after a brief delay, copying a figure of two pentagons that intersect to form a diamond, performing either of the first two steps of three-step request, naming at least ten four-legged animals in 30 second, self-reported "trouble keeping mind on things" three or more days per week during the past month, medical history of stroke, peripheral artery disease, coronary artery bypass surgery, body mass index and alcohol consumption.

When the Turku Elderly Study was initiated in the beginning of 1990s, the Finnish version of the CERAD test battery was not yet available. For that reason, the original item “naming ten four-legged animals in 30 second” was replaced with a mathematic exercise “serial sevens” included in Mini-Mental State Examination. In addition, angioplasty was included in coronary artery bypass surgery.

Older adults (aged ≥65 years) with total scores of 0–2, 3–5, and 6 or more have previously been categorized as having a low, moderate, or high risk for developing dementia during a 6-year follow-up (Barnes et al., 2010). In this study, BDRI was categorized as having a low (total scores of 0–2) or at least moderate (≥3) risk because of a low number of those with high risk (*n*=3) for developing dementia.

BDRI used in study II

Risk factor		Points
Age	75–79 years	1
	80–100 years	2
Delayed recall < 2 of 3		2
Incorrectly copying the intersecting pentagons		1
Incorrectly taking or folding the paper		1
Serial seven[a] 0-2 correct		1
Self-reported ‘trouble keeping mind on things’ ≥ 3 days/week during the past month		1
Stroke		1
Peripheral artery disease		1
Coronary artery bypass surgery or angioplasty[b]		1
Body mass index (kg/m^2) < 18.5		1
Lack of current alcohol consumption		1

[a] Serial seven replaced the original item “inability to name 10 for-legged animals in 30 seconds”

[b] Angioplasty included in coronary artery bypass surgery

4.4.3 The Dementia Screening Indicator (DSI)

DSI includes seven items (range 0–56): age, educational level, BMI, presence of type 2 diabetes, history of stroke, need for help in managing money or medications, and depressive symptoms (report that “everything was an effort” ≥ 3 days per week over the past week) or current anti-depressive medication. Participants scoring 22 or more points have been classified as having a high risk for dementia in 65- to 79-year-olds during a 6-year follow-up.

DSI used in study II

Risk factor		Points
Age	1 point per year above age 65 e.g., 65 years = 0, 70 years = 5	0–14
Education <12 years		9
Body mass index (kg/m^2) <18.5		8
Type 2 diabetes		3
Stroke		6
Need for help in managing money or medications ≥ 3 days per week during the past month		10
Use of anti-depressant medications or self-rated feelings of depression ≥ 3 days per week during the past week		6

4.5 Incidence of dementia in the Study III

The incidence of dementia (ICD-10 codes F00–03 and G30) was obtained from the provincial medical records of the city of Turku and data of mortality from the official Finnish Cause of Death Registry. The data from the registers were acquired using the unique personal identification numbers. The data were available until December 31, 2016. Participants with diagnosed dementia at baseline (*n*=17) were excluded from analyses of dementia incidence (*n*=943), and participants with dementia at baseline or missing data of BDRI (*n*=60) were excluded from analyses for association of BDRI and incident dementia leaving 883 participants, 354 men and 529 women, eligible for these analyses.

4.6 Long-term care and potential predictive factors for the future long-term care in the Study IV and V

Long-term care was defined as an entry into a nursing home or sheltered housing with 24-hour care at any time during the 22-year follow-up, beginning in January 1991. Possible short-term care was not included. Data of long-term care were gathered from the official provincial registers.

Potential predictive factors for long-term care were identified based on their clinical significance and the 1920 and the 1940 birth cohorts were compared in terms of these factors. Sociodemographic and socio-economic variables included gender, marital status, living alone, education, and previous work. Health status variables included self-rated health, self-rated memory compared to other older people, cardiovascular diseases, weight change during the previous five years, and lack of appetite. Psychosocial status was assessed with questions concerning life satisfaction, loneliness, and feelings of depression. Physical status included questions concerning the number of falls during the previous year, difficulties to walk 500 meters, independent daily outdoor exercise, difficulties to move at home, and functional ability. A fall was defined as an event that results in a person unintentionally coming to rest on the ground, floor, or other lower level with or without loss of consciousness or injury (Rubenstein et al., 1990). Need for help was measured with the following variables: the need for daily help in both ADLs and IADLs, having someone who helps when needed, getting help from relatives at least once a week, and the use of domestic help and/or home nursing (public or private) at least once a week. Health behaviors were measured with questions concerning frequency of alcohol consumption and smoking.

4.7 Statistical analyses and programs

4.7.1 Study I

The Chi-square test and Fisher's exact test were used for comparing the differences in the proportions between the groups. Variance analysis was used for comparison of the means of lipid, glucose, BMI, and blood pressure levels. Statistical analyses were performed with the NCSS 2007 statistical package and p values less than 0.05 were considered statistically significant.

4.7.2 Study II

Differences in dementia risk items and categorized dementia risk level between two cohorts were analyzed by using the Chi-square test and Fisher's exact test. Differences in mean scores of indices were tested by using two-sample t test. For BDRI and DSI, analyses were also conducted separately for men and women because gender was not included in those indices. All statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA), and p values less than 0.05 were considered statistically significant.

4.7.3 Study III

Hazard ratios and their 95% confidence intervals for incidence of dementia was calculated using Cox proportional hazard models. Proportional hazards assumption was tested using Martingale residuals. Death was used as a competing risk in the analyses. The follow-up period was calculated from the baseline measurements to the date of incident dementia, the death of the individual or to the end of the follow-up period. The interaction between gender and BDRI was also tested. All statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA), and p values less than 0.05 were considered statistically significant.

4.7.4 Study IV

Associations of potential predictive factors with long-term care were examined with Cox regression analyses. The follow-up periods were calculated from the baseline measurements to the date of long-term care or to the end of the follow-up period of 22 years. Multivariable Cox regression model included all predictors which significantly predicted or tended to predict ($P<0.10$) long-term care in univariate analysis with the following exceptions: (1) MMSE was included in the multivariable model instead of self-rated memory or self-rated memory compared to others, and (2) independent daily outdoor exercise instead of difficulties to walk 500 m and functional ability to avoid multicollinearity. The results are presented with hazard ratios and their 95% confidence intervals. The proportional hazards assumptions were evaluated with Martingale residuals and the assumptions were met. All statistical analyses were performed using SAS System for Windows, version 9.1 (SAS Institute Inc., Cary, NS, USA), and *p* values less than 0.05 were considered statistically significant.

4.7.5 Study V

Significant predictors in univariate Cox regression analyses among the 1920 birth cohort were examined in the multivariate Cox regression model to predict the future institutionalization rate among the 1940 birth cohort. The parameter estimates and baseline hazard function were derived with the multivariate model among the 1920 birth cohort. Proportional hazards over time were assumed in the prediction model. Proportions of sociodemographic and socioeconomic factors among the 1940 birth cohort were used in the prediction model to predict the institutionalization rates of people aged 80, 85, and 90 years. Predictions were calculated for all older people and according to MMSE score, BMI, and the number of falls during the previous year, which were significant predictors of institutionalization in multivariate analyses among the 1920 birth cohort. All statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA), and *p* values less than 0.05 were considered statistically significant.

4.8 Ethical considerations

The City of Turku ethical committee on health care and the ethical committee of the Hospital district of Southwest Finland approved the study protocols of the Turku Elderly Study (TUVA) and the New Turku Elderly Study (UTUVA). Informed consent was obtained from all participants.

5 Results

5.1 Participants in the TUVA and UTUVA studies

Demographic characteristics of the 1920 and the 1940 birth cohorts at the age of 70 year are presented in tables 7–9. Participants born in 1940 were significantly less likely to be widowed or living alone, they were more educated, and had more often done nonphysical work compared with participants born in 1920. There were significant differences in self-rated health, cardiovascular diseases, self-rated memory compared to other older people, MMSE score, BMI, and a lack of appetite between the cohorts. All these differences, except for BMI, were in favor of the 1940 birth cohort. There was no difference in the self-reported weight change during the previous five years between the cohorts.

In terms of psychosocial status, no significant differences were found in life satisfaction and feeling of depression. Instead, those born in 1920 felt loneliness significantly more frequently than those born in 1940 did. The physical status of the participants also favored the 1940 birth cohort. Although there was no difference in the number of falls during the previous year, there were significantly less participants in the 1940 birth cohort having difficulties moving around at home or walking 500 meters.

The proportion of participants needing daily help was lower among the 1940 birth cohort. Despite this, the proportion of participants who used domestic help and/or home nursing at least once a week was higher among the 1940 birth cohort. The rates of participants having someone who helped when needed were almost the same. Participants in the 1920 birth cohort consumed less alcohol, but there was no difference between smoking habits.

5.2 Cardiovascular morbidity, cardiovascular risk factors and the use of medication

The prevalence of cardiovascular diseases and risk factors, use of medication and cardiovascular risk groups of the 1920 and the 1940 birth cohorts at the age of 70 year are presented in table 10. Among the CV risk factors, blood pressure and lipid values favored those born in 1940, but BMI and fasting glucose favored those born in 1920. Hypertension was less commonly diagnosed in the 1920 birth cohort compared with the 1940 birth cohort (34% vs. 50%), but the mean blood pressure was higher in the 1920 birth cohort (155/85 mmHg vs. 145/84 mmHg). Mean lipid values were overall higher in the 1920 birth cohort. The mean total cholesterol was over 6 mmol/l and the mean LDL-cholesterol over 4 mmol/l, whereas, in the 1940 birth cohort the mean total cholesterol was 5.2 mmol/l and the mean LDL-cholesterol under 3 mmol/l. In both cohorts, all lipid values except triglycerides were higher in women than in men ($p<0.001$). In the 1920 birth cohort, the prevalence of dyslipidemia (LDL-c ≥3 mmol/l) was significantly higher than in the 1940 birth cohort, 86% vs. 45%.

The mean BMI among the 1920 birth cohort was 26.5 kg/m^2 and among the 1940 birth cohort 27.7 kg/m^2. In addition, the proportion of participants with BMI ≥30 kg/m^2 was significantly higher among the 1940 birth cohort (17% vs. 26%). The prevalence of diabetes was almost identical in both cohorts, although the mean fasting glucose value among the 1920 birth cohort was 5.1 mmol/l and among the 1940 birth cohort 6.0 mmol/l. In the 1920 birth cohort, the prevalence of coronary heart disease (25% vs. 11%) and peripheral artery disease (9% vs. 2%) were higher than in the 1940 birth cohort, but there was no significant difference in the prevalence of the previous stroke and transient ischemic attack.

Differences in the use of medication between the 1920 and the 1940 birth cohorts were significant. Of the 1920 birth cohort, every third did not use any medication, while of the 1940 birth cohort over 90% of participants used some medication. Overall, the 1940 birth cohort used more CV medications. Of the 1920 birth cohort versus the 1940 birth cohort, 45% vs. 57%, used some cardiovascular medication, 1% vs. 36% used statins, 10% vs. 15% used antidiabetic medication, 41% vs. 56% used antihypertensive medication, and 18% vs. 37% used antithrombotic medication.

In the 1920 birth cohort, 42% were estimated to have a high cardiovascular risk while the corresponding estimate among the 1940 birth cohort was 29%. Mean cholesterol levels of statin users and non-users among the 1940 birth cohort are presented in table 11. One-third of the 1940 birth cohort used statins, and users (n=339) had significantly lower values of total and LDL-cholesterol, and higher HDL-cholesterol than non-users. Of all high-risk persons in the 1940 birth cohort (n=272), 63% used statins.

Table 7. Sociodemographic and socioeconomic factors of the 1920 and the 1940 birth cohort at the age of 70 years.

Characteristics, *n* (%)	**1920 birth cohort, *n*=1032[a] (%)**	**1940 birth cohort, *n*=960[a] (%)**	***p-value***
Sociodemographic and socioeconomic factors			
Gender			
Men	370 (36)	388 (41)	
Women	662 (64)	568 (59)	0.034
Marital status			
Married or living together	541 (53)	613 (65)	
Living alone or divorced	163 (16)	212 (22)	
Widowed	323 (31)	126 (13)	<0.001
Living alone			
No	599 (58)	620 (65)	
Yes	430 (42)	336 (35)	0.002
Education			
High school or more	191 (19)	428 (45)	
Average or less[b]	812 (81)	519 (55)	<0.001
Previous work			
Nonphysical	296 (40)	794 (83)	
Physical	448 (60)	157 (17)	<0.001
Need for help			
Need for daily help in ADLs and/or IADLs			
No	944 (92)	902 (95)	
Yes	79 (8)	49 (5)	0.019
Having someone who helps when needed			
Yes	826 (81)	742 (79)	
No	189 (19)	193 (21)	0.261
Domestic help and/or home nursing at least once a week[c]			
No	988 (96)	868 (91)	
Yes	37 (4)	86 (9)	<0.001

[a] Total number; missing values are excluded when counting the proportions of each characteristic.
[b] Average = 4–8 years of elementary school or primary school.
[c] Includes both public and private domestic help and/or home nursing.

Table 8. Health status and health behavior of the 1920 and the 1940 birth cohort at the age of 70 years.

Characteristics, *n* (%)	**1920 birth cohort, *n*=1032[a] (%)**	**1940 birth cohort, *n*=960[a] (%)**	***p-value***
Health status			
Self-rated health			
Healthy or rather healthy	747 (74)	841 (88)	
Sick or very sick	261 (26)	111 (12)	<0.001
Self-rated memory compared to other older people			
Better	163 (16)	180 (19)	
Same	564 (56)	697 (74)	
Worse	288 (28)	69 (7)	<0.001
Mini-Mental State Examination score			
27-30	672 (65)	778 (84)	
≤26	356 (35)	144 (16)	<0.001
Weight change during the previous 5 years			
No change	578 (57)	562 (59)	
Increased	261 (26)	252 (27)	
Decreased	173 (17)	130 (14)	0.127
Body mass index kg/m^2			
<25	297 (38)	257 (28)	
25.0-29.9	354 (45)	427 (46)	
≥30	134 (17)	238 (26)	<0.001
Lack of appetite			
Never	907 (90)	894 (94)	
Sometimes or daily	97 (10)	56 (6)	0.002
Health behavior			
Alcohol consumption			
Never	391 (38)	163 (17)	<0.001
Smoking			
Never smoked	583 (57)	529 (56)	
Stopped smoking	324 (32)	309 (32)	
Current	116 (11)	113 (12)	0.822

[a] Total number; missing values are excluded when counting the proportions of each characteristic.

Table 9. Psychosocial and physical status of the 1920 and the 1940 birth cohort at the age of 70 years.

Characteristics, *n* (%)	**1920 birth cohort, *n*=1032[a] (%)**	**1940 birth cohort, *n*=960[a] (%)**	***p-value***
Psychosocial status			
Life satisfaction			
Yes	954 (94)	902 (95)	
No	57 (6)	47 (5)	0.499
Loneliness			
Seldom or never	748 (74)	779 (82)	
Sometimes or always	266 (26)	174 (18)	<0.001
Feeling of depression			
Seldom or never	684 (67)	652 (68)	
Sometimes or always	332 (33)	302 (32)	0.628
Physical status			
Number of falls during the previous year			
None	731 (74)	721 (78)	
1-2 falls	212 (21)	167 (18)	
Several falls	51 (5)	40 (4)	0.108
Difficulties walking 500 m			
No	834 (81)	923 (97)	
Yes	198 (18)	32 (3)	<0.001
Independent daily outdoor exercise			
No	110 (11)	78 (8)	
Yes	908 (89)	878 (92)	0.045
Difficulties moving around at home			
No	984 (95)	956 (100)	
Yes	48 (5)	0 (0)	<0.001

[a] Total number; missing values are excluded when counting the proportions of each characteristic.

Table 10. The prevalence of cardiovascular diseases and risk factors, use of medication and cardiovascular risk groups of the 1920 and the 1940 birth cohorts at the age of 70 years.

Characteristics, *n* (%)	**1920 birth cohort, *n*=1032[a]**	**1940 birth cohort, *n*=960[a]**	***p-value***
Blood pressure (mmHg), mean (±SD)			
Systolic	155 (21)	145 (16)	<0.001
Diastolic	85 (10)	84 (9)	<0.05
Body mass index (kg/m^{2}), mean (±SD)	26.5 (4.0)	27.7 (4.7)	<0.001
Fasting glucose (mmol/l), mean (±SD)	5.1 (1.2)	6.0 (0.9)	<0.001
Fasting lipid values (mmol/l), mean (±SD)			
Total cholesterol	6.1 (1.2)	5.2 (1.0)	<0.001
LDL-cholesterol	4.1 (1.0)	2.9 (0.9)	<0.001
HDL-cholesterol	1.4 (0.4)[b]	1.7 (0.5)	<0.001
Triglycerides	1.4 (0.8)	1.3 (0.6)	<0.001
Cardiovascular diseases, *n* (%)			
Coronary heart disease	257 (25)	104 (11)	<0.001
Stroke/transient ischemic attack	94 (10)	86 (9)	0.7
Peripheral artery disease	93 (9)	18 (2)	<0.001
Diabetes	140 (14)	146 (15)	0.3
Hypertension	345 (34)	479 (50)	<0.001
Dyslipidemia (LDL-c ≥3 mmol/l)	794 (86)	413 (45)	<0.001
Use of medication[c], *n* (%)			
Any medication	706 (68)	886 (92)	<0.001
Cardiovascular medication	450 (45)	551 (57)	<0.001
Statin	9 (1)	339 (36)	<0.001
Antidiabetic medication	103 (10)	143 (15)	<0.001
Antihypertensive	420 (41)	534 (56)	<0.001
Antithrombotic medication	184 (18)	358 (37)	<0.001
Cardiovascular risk group, *n* (%)	(*n*=1016[d])	(*n*=956[d])	
High risk	430 (42)	277 (29)	<0.001
Moderate risk	207 (20)	359 (38)	
Low risk	379 (37)	317 (33)	

[a]Total number; missing values are excluded when counting the proportions of each characteristic.
[b]Values of the 1920 cohort raised by 5% to eliminate the difference of the measurement methods.
[c] ATC codes; CV medication C01, C02, C03, C07, C08, C09. Statins C10, fibrates excluded. Antidiabetic medication A10. Antihypertensive medication C02, C03, C07, C08, C09. Antithrombotic medication B01.
[d]Total number reduced due to missed values.
Pearson's χ^2 and fisher's exact test for comparison of proportions
Analysis of variance for comparisons of means

Table 11. Cholesterol values of statin users and non-users among the 1940 birth cohort.

All, *n*=908[a]	**Non-users**		**Statin users**	
	Female, *n*=352	Male, *n*=233	Female, *n=182*	Male, *n*=141
Fasting lipid values (mmol/l), mean (±SD)				
Total cholesterol	5.7 (0.9)	5.2 (0.9)	4.9 (0.9)	4.4 (0.9)
LDL-cholesterol	3.3 (0.8)	3.1 (0.9)	2.5 (0.8)	2.2 (0.7
HDL-cholesterol	1.9 (0.5)	1.5 (0.4)	1.7 (0.5)	1.5 (0.4)
Triglycerides	1.2 (0.6)	1.3 (0.7)	1.4 (0.6)	1.4 (0.6)

[a]Total number with data on lipid values.

5.3 Dementia risk indices among the 1920 and 1940 birth cohorts at the age of 70 years

Altogether, 1,516, 1,598 and 1,462 participants were included in the comparison of dementia risk with the CAIDE Dementia Risk Score (CAIDE), the Brief Dementia Risk Index (BDRI) and the Dementia Screening Indicator (DSI) between the cohorts, respectively. The differences in proportions of participants (cohorts combined) categorized as having an increased risk for developing dementia were distinct. According to these three indices, 96% (CAIDE), 27% (BDRI), and 6% (DSI) of 70-year-old participants had moderate or high risk for developing dementia. Characteristics of CAIDE, BDRI, and DSI are presented in tables 12–14.

According to all examined indices, the total risk scores of the 1920 birth cohort were significantly higher than of the 1940 birth cohort. The proportion of participants with an increased risk for developing dementia instead was significantly higher in earlier than in later born cohort according to categorized CAIDE (99% and 94%, respectively, $p<0.001$) and BDRI (41% and 15%, $p<0.001$), but not according to DSI (5% and 6%, $p=0.184$).

BDRI and DSI were also analyzed separately in women and men, because gender is not included in either index. According to BDRI, 38% and 9% ($p<0.001$) of women in the 1920 and in the 1940 birth cohort, respectively, had moderate or high risk for dementia. Corresponding proportions for men were 47% and 23% ($p<0.001$). In addition, the total scores of BDRI were significantly higher in the 1920 birth cohort compared with the 1940 birth cohort both in women [mean 2.10 points (SD 1.36) and 1.35 points (SD 0.92), respectively, $p<0.001$] and in men [mean 2.41 points (SD 1.30) and 1.84 points (SD 1.20), $p<0.001$]. According to DSI, significant difference was found only in total scores among women [15.06 points (SD 3.56) in the 1920 birth cohort and 13.68 points (SD 5.15) in the 1940 birth cohort, $p<0.001$].

The association of the BDRI and incidence of dementia was examined among the 1940 birth cohort. During a five-year follow-up [mean 5.0 years (SD 0.9), range

0.2–5.8] the rate of dementia incidence was 4.9%. From the 943 participants, 46 developed dementia and 66 (7.0%) died. Of those who died, only two developed dementia. The mean age at the onset of dementia was 74.7 years (SD 1.5) with the age range of 71.4–76.9 years. Having at least moderate risk according to BDRI significantly was associated with incident dementia (HR 3.18, 95% CI: 1.71 to 5.92, $p<0.001$), also after adjustment with education level (2.93, 1.52 to 5.64, $p=0.001$). No interaction between gender and BDRI was found.

Table 12. Characteristics of CAIDE Dementia Risk Score in the 1920 and in the 1940 birth cohort.

CAIDE Dementia Risk Score	Points	1920 cohort *n*=719 (%)	1940 cohort *n*=797 (%)	*p*-value
Age >53 years	4	719 (100)	797 (100)	1.000
Education (years)				< 0.001
≥10	0	50 (7)	169 (21)	
7–9	2	88 (14)	183 (23)	
<7	3	570 (79)	445 (56)	
Male	1	230 (32)	328 (41)	< 0.001
Systolic BP >140 mmHg	2	513 (71)	516 (65)	0.006
Body mass index >30 kg/m^2	2	115 (16)	194 (24)	< 0.001
Total cholesterol >6.5 mmol/L	2	241 (34)	80 (10)	< 0.001
Physical inactivity	1	35 (5)	27 (3)	0.143
Increased risk for dementia	≥6	711 (99)	746 (94)	< 0.001
Total score, mean (SD)		9.39 (1.75)	8.53 (1.99)	< 0.001

Table 13. Characteristics of the Brief Dementia Risk Index in the 1920 and in the 1940 birth cohort.

The Brief Dementia Risk Index	Points	1920 cohort *n*=794 (%)	1940 cohort *n*=894 (%)	*p*-value
Age <75 years	0	704 (100)	894 (100)	1.000
Delayed recall, <2 of 3 words	2	323 (46)	96 (11)	< 0.001
Incorrectly copying intersecting pentagons	1	100 (14)	56 (6)	< 0.001
Incorrectly taking or folding a paper	1	9 (1)	5 (1)	0.176
Serial seven[a], <3 of 5 correct	1	323 (46)	96 (11)	0.422
Self-reported ‘trouble keeping mind on things’ often or almost always	1	131 (19)	154 (17)	0.474
Stroke	1	71 (10)	80 (9)	0.441
Peripheral artery disease	1	55 (8)	16 (2)	< 0.001
Coronary artery bypass surgery[b]	1	9 (1)	49 (5)	< 0.001
Body mass index <18.5 kg/m^2	1	7 (1)	6 (1)	0.578
Lack of current alcohol consumption	1	447 (63)	743 (83)	< 0.001
Risk level according to BDRI				
Low	0–2	415 (59)	759 (85)	
Moderate	3–5	282 (40)	128 (14)	
High	≥6	7 (1)	7 (1)	
Total score, mean (SD)		2.20 (1.35)	1.55 (1.07)	< 0.001

[a]A mathematic exercise to replace the original characteristic “inability to name 10 four-legged animals in 30 s”
[b]Includes also angioplasty

Table 14. Characteristics of the Dementia Screening Indicator in the 1920 and in the 1940 birth cohort.

The Dementia Screening Indicator	Points	1920 cohort *n*=631 (%)	1940 cohort *n*=831 (%)	*p*-value
Age of 70 years	5	631 (100)	831 (100)	1.000
Less than 12 years of education	9	590 (94)	644 (78)	< 0.001
Body mass index <18.5 kg/m^2	8	5 (1)	6 (1)	1.000
Type 2 diabetes	3	76 (12)	138 (17)	0.015
Stroke	6	67 (11)	77 (9)	0.390
Need for help in managing money or medications	10	16 (3)	25 (3)	0.588
Depressive symptoms[a]	6	30 (5)	76 (9)	0.001
Increased risk for dementia	≥22	30 (5)	53 (6)	0.184
Total score, mean (SD)		15.02 (3.94)	13.94 (5.23)	< 0.001

[a]Use of anti-depressant medications or self-rated feelings of depression

5.4 Factors predicting long-term care in home-dwelling 70-year-olds

A total of 227 participants (22.0%) were institutionalized during the 22-year follow-up, beginning in January 1991. Among the 1920 birth cohort, the mean age for entry to the long-term care was 85.3 years with age range of 73.1–92.3 years. Significant predictors of long-term care are shown in table 15. In univariate Cox regression analysis the following predicted long-term care during the 22-year follow-up: 1) self-rated health (feeling oneself sick or very sick), 2) impaired or poor self-rated memory, 3) worse self-rated memory compared to others, 4) impaired cognitive function (MMSE ≤26), 5) BMI <25 kg/m^2 (compared with both BMI of 25.0–29.9, and that of ≥30 kg/m^2), 6) having lack of appetite, 7) having feelings of loneliness, 8) depression at least sometimes, 9) having several falls during the previous year (compared with no falls), and 10) being functionally dependent. Instead, socio-demographic, and socio-economic factors, CVDs, health behaviors, need for daily help, incontinence, and self-reported weight change were not associated with long-term care.

In multivariable Cox regression model (table 16), significant predictors of institutionalization were only impaired cognitive function (MMSE ≤26), BMI <25 kg/m^2, and having several falls during the previous year.

5.5 Prediction of the future need for long-term care in the 1940 birth cohort

In the 1940 birth cohort, the predicted rates of those needing long-term care and by MMSE, BMI, and number of falls at the ages of 80 (year 2020), 85 (year 2025), and 90 (year 2030) are presented in the table 17. At every age (80, 85, and 90 years), the predicted rates of participants needing long-term care were about two-fold among those with MMSE scores ≤26 compared to those with scores 27–30. In terms of BMI, the rates were lowest among those with BMI 25.0–29.9 and highest among those with BMI <25. The predicted institutionalization rate of participants with BMI <25 was about two-fold compared to those with BMI 25.0–29.9. Among participants having had several falls, the predicted rates were about two-fold compared to participants with one or two falls and about three-fold compared to participants with no falls during the previous year.

Table 15. Unadjusted hazard ratios (HR) and their 95% confidence intervals (95% CI) for predictive factors for long-term care among the 1920 birth cohort (*n* = 1032).

	n	**HR**	**95% CI**	***p*-value**
Health status				
Self-rated health (sick or very sick vs. healthy or rather healthy)	1008	**1.50**	**1.09 – 2.06**	**0.013**
Self-rated memory (impaired or poor vs. good)	1021	**1.62**	**1.25 – 2.11**	**< 0.001**
Self-rated memory compared to others	1015			
Same vs. better		1.06	0.72 – 1.56	0.756
Worse vs. better		**1.57**	**1.04 – 2.38**	**0.034**
Mini-Mental State Examination (≤26 vs. 27–30)	1028	**1.69**	**1.30 – 2.20**	**< 0.001**
Body mass index kg/m^2	785			
<25 vs. 25.0–29.9		**1.54**	**1.13 – 2.09**	**0.006**
<25 vs. ≥30		1.36	0.92 – 2.03	0.127
≥30 vs. 25.0–29.9		1.13	0.75 – 1.70	0.562
Lack of appetite (sometimes or daily vs. never)	1004	**1.59**	**1.01 – 2.49**	**0.044**
Psychosocial status				
Life satisfaction (no vs. yes)	1011	1.41	0.75 – 2.66	0.290
Loneliness (sometimes or always vs. seldom or never)	1014	**1.41**	**1.06 – 1.88**	**0.018**
Feeling depressed (sometimes or always vs. seldom or never)	1016	**1.47**	**1.12 – 1.93**	**0.005**
Zung Depression Scale (≥45 vs. 20–44)	1031	1.26	0.88 – 1.80	0.211
Physical status				
Number of falls during the previous year	994			
1-2 falls vs. none		1.29	0.94 – 1.77	0.110
Several falls vs. none		**1.90**	**1.08 – 3.35**	**0.027**
Difficulties to walk 500 m (yes vs. no)	1032	1.35	0.96 – 1.92	0.089
Independent daily outdoor exercise (no vs. yes)	1018	1.58	0.99 – 2.53	0.057
Difficulties to move at home (yes vs. no)	1032	1.28	0.68 – 2.41	0.447
Functional ability (needs help vs. independent)	1018	**1.44**	**1.01 – 2.05**	**0.045**
Need for help				
Need of daily help (yes vs. no)	1023	1.77	0.99 – 3.18	0.054
Having someone who helps when needed (no vs. yes)	1015	1.32	0.97 – 1.78	0.077
Getting help from relatives at least once a week (yes vs. no)	999	1.00	0.72 – 1.38	1.00
Use of domestic help and/or home nursing at least once a week (yes vs. no)	1025	2.01	0.89 – 4.53	0.092

Statistically significant predictive factors are bolded

Table 16. Adjusted hazard ratios (HR) and their 95% confidence intervals (95% CI) for predictive factors for long-term among the 1920 birth cohort (*n*=698).

	HR	95% CI	*p*-value
Self-rated health (sick or very sick vs. healthy or rather healthy)	1.13	0.74 – 1.72	0.570
Mini-Mental State Examination (≤26 vs. 27–30)	**1.71**	**1.24 – 2.36**	**0.001**
Body mass index kg/m^2			
<25 vs. 25.0–29.9	**1.88**	**1.32 – 2.67**	**< 0.001**
<25 vs. ≥30	**1.66**	**1.05 – 2.60**	**0.029**
≥30 vs. 25.0–29.9	1.14	0.72 – 1.79	0.586
Lack of appetite (sometimes or daily vs. never)	1.00	0.57 – 1.75	0.995
Loneliness (sometimes or always vs. seldom or never)	1.02	0.66 – 1.60	0.923
Feeling depressed (sometimes or always vs. seldom or never)	1.32	0.90 – 1.93	0.153
Number of falls during the previous year			
1–2 falls vs. none	1.34	0.94 – 1.92	0.105
Several falls vs. none	**2.50**	**1.28 – 4.90**	**0.007**
Need of daily help (yes vs. no)	1.20	0.37 – 3.90	0.760

Statistically significant predictive factors are bolded

Table 17. The predicted rates (%) of those needing long-term care in the total 1940 birth cohort, by MMSE, BMI, and number of falls during the previous year, at the age of 80, 85, and 90 years.

Age	Overall	MMSE		BMI			Number of falls		
		27–30	≤26	≥30	25–29.9	<25	None	1–2	≥3
80	1.8	1.6	3.0	1.8	1.4	2.5	1.5	2.2	5.3
85	10.4	9.3	16.8	10.3	8.1	14.3	9.0	12.5	27.5
90	26.0	23.7	38.8	25.9	20.9	34.3	23.1	30.9	57

6 Discussion

This thesis researched secular changes in cardiovascular morbidity, cardiovascular risk factor profiles, and dementia risk indices between two birth cohorts of 70-year-old born 20 years apart. The association with the Brief Dementia Risk Index and incidence of dementia among community-dwelling 70-year-olds during a five-year follow-up was examined. Furthermore, predictive factors on long-term care were examined and the future need for long-term care for Finnish older people was predicted. Overall, the 1940 birth cohort performed significantly better than the 1920 birth cohort in health, psychosocial, and physical status at the age of 70 years. In terms of CVD morbidity, the 1940 birth cohort was healthier, and their dementia risk determined by the CAIDE and the BDRI risk scores was lower compared with the 1920 birth cohort. Among the 1940 birth cohort, those with at least moderate risk for developing dementia according to the BDRI had a three-fold dementia incidence risk compared to those with that of low risk. According to the baseline characteristics, significant predictors of long-term care were impaired cognitive function, low BMI, and having several falls during the previous year.

6.1 Cardiovascular morbidity, risk factor profiles and prevalence of statin use

The prevalence of coronary heart disease (25% vs 11%) and peripheral artery disease (9% vs 2%) were lower among the 1940 birth cohort. Globally and nationally, the trend has been similar; the prevalence of vascular diseases has decreased (Amini et al., 2021; Koponen et al., 2018; Wilkins et al., 2017; World Health Organization, 2022). In this study, lipid profiles, and blood pressure levels favoured those born in 1940. Better lipid profiles included lower total cholesterol and LDL-cholesterol, and higher HDL-cholesterol corresponding the improvements observed in international studies (Farzadfar et al., 2011) and nationally in the Finnish North Karelia Project during past decades (Vartiainen, 2018; Vartiainen et al., 2010). According to the Healthy Finland Survey in 2022–2023, the prevalence of elevated LDL-cholesterol has continued to decrease among older adults (Vartiainen et al., 2024).

The diagnosis of hypertension (34% vs 50%) and use of antihypertensive medication (41% vs 56%) were significantly more common among the 1940 birth cohort, although mean BP levels in the 1920 birth cohort were higher. In the beginning of 1990s, threshold of BP for treating was noticeably higher than during the 2000s. For those born in 1920, antihypertensive medication was typically prescribed when the BP was over 160/90 mmHg. During the 2000s, national guidelines have recommended treatment already at level 140/90 mmHg (Williams, 2009). These changes in diagnostic and treatment of hypertension led to an increasing number of participants with better controlled and more often treated hypertension among the 1940 birth cohort. Globally and among the entire Finnish adult population, the trend has been similar; systolic BP levels have dropped significantly since the 1970s (NCD Risk Factor Collaboration, 2017; Vartiainen et al., 2010). In the 21st century, the positive development has slowed down (Borodulin et al., 2013; Koponen et al., 2018; S. Koskinen et al., 2012; Laatikainen et al., 2013; Vartiainen et al., 2010).

Smoking habits did not differ between the cohorts. Among the 1920 birth cohort 11% and among the 1940 birth 12% of participants were current smokers, including those who do not smoke daily but weekly. In Finland, percentage of daily smokers aged 65–84 years has also been stable, around 7% (H. Koskinen & Virtanen, 2022). In contrast, globally and for example in the USA and in Australia smoking prevalence among older adults aged 60 years and over has declined over the past two decades (Hunt et al., 2023; The Cancer Council Victoria, 2020; World Health Organization, 2021b). Regular alcohol consumption, on the other hand, was more common among the 1940 birth cohort. The proportion of those who did not consume alcohol was 38% among the 1920 birth cohort and 17% among the 1940 birth cohort. This is consistent with the national data. Alcohol consumption among people aged 65 years and over started to increase in the 1990s, the growth continued until the 2010s, and has been stable during the past decade (Mäkelä et al., 2018). For both cohorts, possible comorbidities related to alcohol use are not known, but regular alcohol consumption may have influenced to the higher HDL-cholesterol level of the 1940 birth cohort.

The prevalence of stroke and transient ischemic attack were almost identical in both cohorts; 10% among the 1920 birth cohort and 9% among the 1940 birth cohort. It is well known that stroke prevalence increases with age and age is the predominant non-modifiable risk factor for stroke (Boehme et al., 2017). Due to reduction in case fatality after stroke and improved diagnostic methods, the stroke prevalence would have been expected to increase among the later born cohort as it was in a Swedish study (Zhi et al., 2013). In that study, two birth cohorts of 75-years old were examined in 1976 and 2006. The stroke prevalence in the later-born cohort was higher although the prevalence of any CVDs was lower (Zhi et al., 2013). The incidence of stroke doubles for each decade after age of 55 (Roger et al., 2012), but peaks after age of 70 (Béjot, 2022; Boix et al., 2006; Teh et al., 2018). For example, in the US National Health and Nutrition Examination Survey III (1988–1994), the stroke prevalence among the population older than age 75 years was more than twice that of the 60–74 age group (Muntner et al., 2002). Thereby, it is possible that the differences in stroke prevalence among 70-year-old cohorts are not as obvious, and this might partially explain the lack of increase in stroke prevalence in this study.

The prevalence of type 2 diabetes was almost identical in both cohorts (14% vs 15%). It should be noted that until 1999, the threshold value of fasting glucose for the diagnosis of diabetes was 7.8 mmol/l instead of current value of 7.0 mmol/l. Nevertheless, the 1940 birth cohort had significantly higher fasting glucose levels (mean 5.1 mmol/l vs 6.0 mmol/), and the use of antidiabetic medication was more common among the 1940 birth cohort (10% vs 15%). These findings indicate that the prevalence of DM in fact was greater in the 1940 birth cohort. For those born in 1940, the prevalence of DM was corresponding to findings in the Finnish Health 2011 survey. In that study, the prevalence of DM among men aged 65–74 years old was 19.5% and among women 14.4% (S. Koskinen et al., 2012). The prevalence of obesity (BMI >30 kg/m^2) was more common, and the mean BMI was higher among the 1940 birth compared with the 1920 birth cohort. However, the mean BMI of both cohorts was in the optimal range (25–29.9 kg/m^2) considered for older adults (Kvamme et al., 2012). Concerning the 1940 birth cohort, findings are comparable with the Finnish Health 2011 survey, where the mean BMI among men aged 65–74 years old was 27.5 kg/m^2 and among women 28.3 kg/m^2 (S. Koskinen et al., 2012). In addition, the prevalence of obesity was comparable among the age group of 65–74 years old. In men the prevalence was 24.9% and in women 35.4%. Worldwide and nationally the increasing trend of both prevalence and incidence of DM (J. Liu et al., 2020; Wild et al., 2004) and obesity (Fakhouri & Kit, 2012; Ng et al., 2014; Peralta et al., 2018; Vartiainen et al., 2010) also among the older people have been similar. In Finland, adult obesity (BMI >30 kg/m^2) has increased significantly over the past two decades. In 1997, 15% of adults (aged 30 years and over) were obese. In 2017, the corresponding value was 23% (Koponen et al., 2018).

Multivariable CVD risk assessment tools are used to estimate an individual's risk of CVD. The risk estimation is typically based on different modifiable and non-modifiable risk factors. In this study, classification was based on whether participants already had an existing CVD (CHD, stroke/TIA, PAD), DM, prevalent hypertension and/or they used cardiovascular medication. According to estimated CVD event risk, a greater proportion of the 1920 birth cohort compared with the 1940 birth cohort belonged to the high-risk group (42% vs 29%). A change from high to lower risk is in line with findings from USA and Europe using various risk assessment tools (Alageel et al., 2016; Ford, 2013; Nilsen et al., 2019). Nevertheless, the proportion of participants at high risk has varied a lot depending on the used risk score and whether additional comorbidities has been considered (Diederichs et al., 2018; Nilsen et al., 2019).

The main contributors to better CVD morbidity among the 1940 birth cohort were probably the increased use of preventive CV medication and improvements in lifestyle factors (Borodulin et al., 2015; Hopstock et al., 2015, 2017; Vartiainen et al., 2010). Especially the use of statins and antihypertensives became more common during the 2000s. In this study, the proportion of statin users increased from 1% to 36% between the cohorts. Among the 1940 birth cohort, the use of statins was most common among the people estimated to have a high cardiovascular event risk. Unfortunately, still one-third in the high-risk group did not use statins at all.

6.2 Secular changes in dementia risk indices and the association with the Brief Dementia Risk Index and incidence of dementia

Dementia risk among two birth cohorts of 70-year-olds born 20 years apart was assessed with three dementia risk model: 1) The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score (Kivipelto et al., 2006), 2) The Brief Dementia Risk Index (BDRI) (Barnes et al., 2010), and 3) The Dementia Screening Indicator (DSI) (Barnes et al., 2014). The total risk scores of the 1940 birth cohort were significantly lower than those of the 1920 birth cohort according to all three indices. Thus, dementia risk, assessed by using dementia risk indices, has decreased among Finnish community-dwelling older adults during the 1990s–2010s.

There is evidence of decreasing age-specific incidence and stable or decreasing age-specific prevalence of dementia in Europe and in the USA (Ahmadi-Abhari et al., 2017; Qiu & Fratiglioni, 2018; Winblad et al., 2016; Wolters et al., 2020). Explanations for the decreasing incidence of dementia are suggested to be, for example, higher education, brain-healthy lifestyle, improvements in living conditions and social welfare, as well as better treatment of major vascular risk factors and better access to health care interventions such as blood pressure control and antithrombotic medication. Nevertheless, it is not clear which of the possible key risk factors of dementia are cause of declining temporal trends in dementia incidence. Probably decades of cardiovascular risk management have had remarkable effects on brain (Pase et al., 2017). This is also supported by reduction of small-vessel disease on brain imaging in more recent years (Schrijvers et al., 2012). Another major change over the past century has been improved access to education that could explain decreasing incidence of dementia over time (EClipSE Collaborative Members et al., 2010). Unfortunately, like heart disease (Jones & Greene, 2013), the rise on a global scale of obesity (NCD Risk Factor Collaboration, 2016), diabetes (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017), and hypertension (NCD Risk Factor Collaboration, 2017) may reverse trends in dementia occurrence over the coming decades.

In this study, proportion of participants with an elevated risk for dementia varied a lot based on the index used. According to CAIDE, 99% of participants in the 1920 birth cohort and 94% in the 1940 birth cohort had moderate or high risk for dementia. Conversely, according to BDRI the corresponding proportions were 41% and 15%, and according to DSI only 5% and 6%. The most significant reason for such large differences between the indices is in the items highlighted in the scores.

CAIDE was originally developed for a middle-aged population (Kivipelto et al., 2006). Based on this study, the predictive value of the CAIDE score was poor among the 70-year-old population. This is in line with previous studies conducted among older populations (Anstey et al., 2014; Hooshmand et al., 2018; Licher et al., 2018; Solomon & Soininen, 2015; E. Y. Tang et al., 2015). In this study, all participants received the highest score for age already at the baseline. CAIDE also highlights the role of vascular factors, which have found to have inverse associations with dementia among older age groups (Mielke et al., 2005; E. Y. Tang et al., 2015; Tolppanen et al., 2014). However, a late-life CAIDE dementia index has also been developed. This index is based on a supervised machine learning method, which can handle large amounts of data, structure risk factors into groups and give a comprehensive overview of an individual's predictive profile pointing the most relevant risk factors (Pekkala et al., 2017). Overall, CAIDE is a good and validated index for mid-life dementia risk prediction (Hou et al., 2019; Ranson et al., 2021), but to implement it among older people has limitations.

All risk indices used in this study are brief and easy to use in primary care settings. Unlike CAIDE, both BDRI and DSI are validated among older population (≥65 years of age). Therefore, they are expected to be more appropriate instruments to identify older individuals with an elevated risk for developing dementia later in life. According to this study, proportion of participants with an increased risk for dementia according to DSI was low in both cohorts. Finding is in line with earlier studies, where the proportions have also been relatively low, ranging from 6 to 27% (Barnes et al., 2014). The main reason is probably related to differences in combinations of risk factors between indices. DSI is a combination of demographic, vascular and lifestyle factors, difficulties in instrumental activities of daily living and depressive symptoms (Barnes et al., 2014). BDRI, instead, includes a combination of age and cognitive, lifestyle and cardiovascular factors, but cognitive items are highlighted (Barnes et al., 2010). In another Finnish study, investigating supervised machine learning method using many heterogeneous factors, cognitive performance was the most important predictor, more predictive than age or vascular factors, for subsequent dementia (Pekkala et al., 2017). Hence, it is possible that DSI underestimates dementia risk and thereby misses older adults with milder cognitive symptoms who should be targeted for cognitive screening. On the other hand, DSI is recommended when dementia risk is assessed only based on modifiable risk factors without cognitive tests (Ranson et al., 2021).

The BDRI is based on the findings in the Cardiovascular Health Cognition Study (CHCS) and is derived from the former published late-life dementia risk index (Barnes et al., 2009, 2010). The baseline studies of the CHCS were carried out during the 1992–1993 around the same time as the 1920 birth cohort in the Turku Elderly Study. In the CHCS, all participants were 65 years and over, and the mean age at baseline was 76 years (Barnes et al., 2010). Although the population in the CHCS was slightly older than the 1920 birth cohort at the baseline, the proportion of individuals with increased dementia risk was almost identical. In the 1920 birth cohort, 41% had moderate or high risk for dementia. In the CHCS, corresponding value was 40%. Based on this, the BDRI was found to be the most applicable instrument in this home-dwelling 70-year-old population.

The association of BDRI and incidence of dementia was analyzed among the 1940 birth cohort. During the five-year follow-up, 4.9% of participants were diagnosed with dementia, and 7% of participants died. Of those who died, only two developed dementia. In the original CHCS population, 14% developed dementia within six-year follow-up, but among the 65–74 age group, the incidence rate was 7%. The main reason for higher incidence rate in the CHCS is probably due to differences in establishment of dementia diagnoses. In the New Turku Elderly Study, information about dementia diagnosed during the follow-up was obtained from the medical records. While in the CHCS, the dementia diagnoses were made based on detailed data collected during the study (Barnes et al., 2009). Among the 1940 birth cohort, those with at least moderate risk for developing dementia according to BDRI had a three-fold dementia incidence risk compared to those with that of low risk during a five-year follow-up. This risk remained after adjustment with education level. No gender differences were found in the association of BDRI and dementia incidence.

The main targets of dementia risk scores are to early identify individuals at high risk, to improve risk perception for patients and physicians, and to help target interventions to improve lifestyle habits to decrease dementia risk. However, dementia risk scores are not yet widely used in clinical settings. Despite numerous dementia risk indices, only few are validated, and it is not always obvious which of them should be used. For example, in the field of CVDs the situation is opposite (Bonner et al., 2019). Perhaps the most well-known example is the Framingham Risk Score (FRS), originally developed to estimate the 10-year coronary heart disease risk on adults (Wilson et al., 1998). Nowadays, FRS is widely used in the USA, and it has extended to subsequent risk scores for cerebrovascular events, peripheral artery disease, and heart failure (D'Agostino et al., 2008). For European population, it is recommended to use the corresponding SCORE2 prediction tool (SCORE2 working group and ESC Cardiovascular risk collaboration, 2021), of which is also available a version for adults aged over 70 years (SCORE2-OP working group and ESC Cardiovascular risk collaboration, 2021). For Finns, the FINRISK-calculator is the primary risk tool concerning risk of acute myocardial infarction or acute disorder of the cerebral circulation within the next ten years (*FINRISK-calculator*, n.d.).

At the individual level, insufficient knowledge that CVDs and dementia share several modifiable risk factors and pessimistic attitude towards possibilities of dementia prevention (Akenine et al., 2020) probably affects how interested people are about their dementia risk. Additionally, people have feelings of fear, shame, and hopelessness in anticipation of developing dementia (Akenine et al., 2020) and there are still stigma and fear toward people with dementia (T. Nguyen & Li, 2020). As the neuropathological features of dementia-related disorders may begin 15 to 20 years before obvious cognitive symptoms, this long preclinical phase may also affect the usability of risk scores. Levels of risk factors may change over time, some factors are more essential in midlife and some in late-life, and some risk factors together increase risk (i.e., combined effect). For example, co-occurrence of hypertension, obesity, hypercholesterolemia and/or physical inactivity in midlife has an additive effect. Similarly, in late-life individuals with brain hypoperfusion profile (chronic heart failure, low pulse pressure, low diastolic pressure) have higher dementia risk (Solomon et al., 2014). According to this study, dementia risk estimates given by different risk indices differ considerably from each other. For this reason, dementia risk index should be chosen based on purpose of use and the target population.

6.3 Factors predicting long-term care and prediction of the future need for long-term care

The future institutionalization rate among the 1940 birth cohort was predicted using data from the 1920 birth cohort. Among the 1920 birth cohort, the rate of institutionalization was 22% during a 22-year follow-up. Increased risk of long-term care was associated independently with impaired cognitive function (MMSE score ≤ 26), low BMI (<25 kg/m^2), and several falls during the previous year before the baseline assessment. Consistent with this study there is strong evidence that institutionalization is basically caused by cognitive and/or functional impairment (Aguero-Torres et al., 2001; Bravell et al., 2009; Gnjidic et al., 2012; Luppa et al., 2012; Luppa, Luck, Matschinger, et al., 2010; Luppa, Luck, Weyerer, et al., 2010; von Bonsdorff et al., 2006). In another Finnish study among dementia-free population aged 75- and 80-year-old, the risk of long-term care during a 10-year follow-up was 4.9 times greater for those who had co-existing mobility limitations and cognitive deficits compared to those with no limitations (von Bonsdorff et al., 2006). The association between cognitive and functional impairment is strong, but one-sided (Luppa, Luck, Weyerer, et al., 2010). This means that severe cognitive impairment leads to limitations in activities of daily living and instrumental activities of daily living, but functional impairment does not result in combined effect of cognitive functions.

Each year about a third of community-dwelling people aged 65 years and over fall (Gillespie et al., 2012). As in some previous studies (Dunn et al., 1993; Tinetti & Williams, 1997) and in more recent study among patients of urgent geriatric outpatient clinic (Salminen et al., 2020), also in this study repeat falls predicted long-term care. Fallers have lower level of physical activity (Jefferis et al., 2014) which may decrease strength and balance and initiate a downward cycle towards losing independence and entering long-term care (Jefferis et al., 2014; Kumar et al., 2016). In this study, BMI less than 25 kg/m^2 compared with both BMI of 25–29.9 and that of ≥30 predicted need for long-term care. This is consistent with several studies showing that "optimal BMI" in the older adults is about 25–30 kg/m^2 (Estrella-Castillo & Gómez-de-Regil, 2019; Janssen & Mark, 2007; Kıskaç et al., 2022; Kvamme et al., 2012; Y. Lee et al., 2014; Locher et al., 2007).

Overall, the 1940 birth cohort performed significantly better than the 1920 birth cohort in health, psychosocial and physical status as in several earlier studies (Christensen et al., 2013; Engberg et al., 2008; Falk et al., 2014; Freedman et al., 2002; Hörder et al., 2015; Litwin et al., 2012; Manton et al., 2006; Pitkälä et al., 2001; Robine, 2006; Wilhelmson et al., 2002; Zunzunegui et al., 2006). Despite these improvements, in the total population, the predicted rates of those needing long-term care in the future increased with age from 1.8% at the age of 80 (year 2020) to 26.0% at the age of 90 (year 2030). The predicted rates were even higher and increased more with age among those with lowered cognitive status, low and high BMI (<25 or ≥ 30), or previous falls. Compared to those with good cognitive status, normal BMI, and no previous falls, the predicted rates were about two- to three-fold. The number of older people, especially the number of those aged over 85 years, is increasing both in Finland and globally (Christensen et al., 2009; Official Statistics of Finland, 2021a; United Nations et al., 2019). Thus, the number of older adults with geriatric syndromes (e.g., dementia, frailty, and falls) is expected to rise (Forma et al., 2017; Sanford et al., 2020; Strandberg et al., 2013), although later cohorts of older people seem to have better functional ability (Kivimäki & Strandberg, 2022).

Geriatric syndromes are associated with increased levels of disability, long-term care, and death, and their human, economic and social impacts are enormous (Cigolle et al., 2007; Strandberg et al., 2013). The Finnish national policy is to allow older adults to live at home and have the services they need provided at home (Finnish Institute for Health and Welfare, 2022b). Accordingly, the proportion of people aged 75 and older living at home has increased from 90% to 93% since the late 1990s

(Finnish Institute for Health and Welfare, 2022a). At the same time, the need for regular home care among the 75 year and older has increased (Finnish Institute for Health and Welfare, 2022c), and service or sheltered housing with 24-hour care and support has replaced the traditional institutional long-term care (Finnish Institute for Health and Welfare, 2022d; National institute for health and welfare, 2014). But structural changes alone do not reduce the need for care as the number of older people increases.

In addition to better health and functional ability, the previously mentioned changes in Finnish old-age policy and changes e.g., in CVD morbidity may have contributed that the proportion of participants living at home in the 1940 birth cohort was higher. They also used domestic help and/or home nursing more frequently, although the proportion of those needing daily help and those living alone was lower compared with the 1920 birth cohort. Nowadays, there are also more home services, both public and private, available. Furthermore, older individuals are used to, more willing, and able to use different kinds of services and help, to ease their everyday life. The results are consistent with the US Second Longitudinal Study of Aging (Y.-M. Chen & Thompson, 2010), that found two significant supportive factors for older people to remain in their communities were the use of paid instrumental activities of daily living personal care services and an awareness of unmet needs. In addition, a Finnish study has found a connection between the utilization of social care services and perceived health. In that study of frail older adults, those who reported improvements in their health status during the preceding year used more frequently social care service (Kehusmaa et al., 2012).

According to this study, it seems that the proportional need of long-term care will decrease or be at least postponed to a higher age. During the 2010s, the national trend has been similar. The proportion of older people in long-term care (service housing with 24-hour care and support and institutional care together) has decreased from 10.3% to 8.0% (Finnish Institute for Health and Welfare, 2022d). On the other hand, the longer people live and the older they die, the more likely they are to need long-term care at the end of their lives (Forma et al., 2017). As the number of oldest-old increases, the absolute need for long-term care in Finland may increase, at least during the last years of life.

Due to cross-sectional study design, this study lacks the data to model any of the compression, expansion, or postponement scenarios. However, the results can be considered in the light of these three scenarios. If a longer survival is accompanied by compression of morbidity, the predicted rates of future need for long-term care are probably going to be lower than predicted in this study. This would affect particularly people aged 80–85 years. Unfortunately, healthy life expectancy has not risen as fast as life expectancy (Salomon et al., 2012; World Health Organization, 2021a) indicating that the compression of morbidity may not occur in near future.

Conversely, the postponement theory is more likely to occur, especially among those aged under 85 (Christensen et al., 2009). In that case, the need for long-term care will probably be lower at the ages of 80 and 85, but higher at the age of 90 years than predicted in this study. This is also in line with the Finnish study showing that long-term care is increasingly concentrated in the last years of life (Forma et al., 2017). The worst scenario is an expansion of morbidity that assumes that years of poor health are added. If this occurs, the rates of those needing long-term care in the future are probably going to be even higher at every age group than predicted in this study.

6.4 Strengths and limitations

The study populations consisted of two birth cohorts of 70-year-olds, participants were born 20 years apart and they lived in the same geographical area, which enhanced the validity of study. Twenty to thirty years is used in many cohort comparison studies as the period to show cohort differences [e.g., (Brailean et al., 2018; Degen et al., 2022; Ikram et al., 2017; Overton et al., 2022; Skoog et al., 2017; Wiberg et al., 2013)]. Nevertheless, during the 20-year period from the early 1990s to the early 2010s there have been socioeconomic, cultural, and social and health care system changes. These changes may have influenced how older people rate their functional status and health, and therefore they have to be considered for self-rated indicators (Hörder et al., 2015).

In this thesis, the most significant biases were related to the questionnaire filled out by the participants themselves. Social-desirability bias means that responders tend to answer questions in a manner they think is favorable to research (Krumpal, 2013). As a result, desirable behaviors are overreported and undesirable behaviors are underreported, which influence the reliability and validity of outcome measures over time and longitudinal response shifts. Self-reported risk factors may be vulnerable to recall bias and interpretation. For example, participants may misremember events from years or decades ago. Information bias may also arise if a relative or a friend of the participant answers the questions on behalf of the participant. The New Turku Elderly Study (the 1940 birth cohort) tried to eliminate above-mentioned biases so that questionnaires were checked together with participants. Thereby, it was possible for the researcher to clarify unclear answers. There may also have been selection bias in the baseline. Thus, it is possible that prevalence of multimorbidity and cognitive decline were more common among non-responders.

Both cohorts were quite large, and participation rates were good and comparable; 70% in the 1920 birth cohort and 73% in the 1940 birth cohort. Only home-dwelling older adults were included in the baseline studies, and therefore the results are not applicable to the older people living in nursing homes. Data on non-responders were not available in any of the sub-studies. Usually, non-responders have poorer health and functional ability than responders, which indicates a healthy population bias on both cohorts (Hörder et al., 2015). The Turku elderly studies (both the 1920 birth cohort and the 1940 birth cohort) were originally designed to evaluate determinants of successful aging, not only predictors of CVDs and dementia. Hence, the risk of participation bias was quite low.

All the variables used in sub-studies are commonly used in population-based studies in Finland [e.g., in the Helsinki Ageing Study (Juva et al., 1993)] and/or internationally, and many of the variables are validated; e.g., MMSE (Spering et al., 2012), BMI (Bahat et al., 2012), falls (Tinetti & Williams, 1997), self-rated 500 meter walk (Guralnik et al., 1994), self-rated health (Jylhä et al., 2006), feeling of loneliness (Russell et al., 1997), and use of alcohol (P. C. Smith et al., 2009). Conversely, the differences in diagnostics of CVDs and cognitive disorders during the baseline studies in 1991 and 2011 were unavoidable. In 1991, several clinicians and nurses in primary health care carried out the baseline studies. In 2011, the study physician and nurse performed all baseline examinations. Despite this, the same criteria in examinations were used. Most of the participants' previous diagnosis were based on their medical records, but diagnoses and prescriptions from private health care were unconfirmable. In some cases, diagnostic criteria, and methods in the 2010s differed from those in the 1990s. These include for example 1) the BP target was higher in 1991 than 20 years later and therefore the prevalence of hypertension diagnosis was lower although the mean BP were higher among the 1920 birth cohort; 2) in 1991 the diagnosis of peripheral artery disease was not always confirmed by the ankle-brachial index or an examination by a specialist vascular surgeon, and 3) due to advanced diagnostic methods, it was possible to examine cognitive symptoms in more detail in the 2010s. In addition, even if diagnostic criteria remain unchanged over time, the diagnosis may change during re-evaluation (Kaunisto et al., 2015; Moum et al., 1997). Due to cross-sectional study design, this thesis cannot confirm changes in functional and health status, only differences between the 1920 and 1940 birth cohorts.

7 Conclusions

The main findings and conclusions of the thesis were:

- The observed changes between the 1920 and the 1940 birth cohorts in cardiovascular disease morbidity and risk of dementia, and predicted need for long-term care were parallel. The 1940 birth cohort had lower cardiovascular disease morbidity, and their dementia risk and future need for long-term care were lower compared with the 1920 birth cohort. These findings suggest that by influencing the risk factors for cardiovascular diseases and dementia, it is possible to reduce the need for long-term care.
- Of the cardiovascular risk factors, blood pressure and cholesterol values declined in the 1940 birth cohort, but the prevalence of diabetes and obesity increased compared with the 1920 birth cohort. The 1940 birth cohort used more cardiovascular medications, but it is unclear whether this will compensate increased cardiovascular risk due to diabetes and obesity.
- The main predictors for need of long-term care were cognitive decline and reduced physical function.
- Despite the better general health and cognitive performance among the 1940 birth cohort, the predicted rates of future need for long-term care were high, especially at the ages of 85 and 90 years among those with impaired cognitive or physical function.
- The Brief Dementia Risk Index predicted incident dementia during a five-year follow-up, and it could be an applicable tool for the identification of older individuals at increased risk of developing dementia in clinical settings.

Future research should examine, if the observed differences in the cardiovascular risk factors, morbidity, and risk of dementia between cohorts will persist, narrow, or widen.

In addition, during the recent years, there have been major changes in the diagnostic of Alzheimer's disease. The new blood-based biomarkers for dementia-related diseases (Angioni et al., 2022) enable better and earlier diagnosis, but we do not know whether the use of these biomarkers is economically possible for example in the primary health care. It is also unclear, if blood-based biomarkers can be used to predict the need for long-term care. Secondly, the new disease modifying anti-amyloid drugs for Alzheimer's disease (Cummings, 2023; Jönsson et al., 2023) can change the course of the Alzheimer's disease, although they do not cure, and they cannot be used for everyone. However, we do not know for example, if cardiovascular diseases will affect drug benefits and risk of side effects, and if anti-amyloid drugs will delay the need for long-term care.

In the field of digital services in healthcare, there has also been changes that may support living at home longer, and digital cognitive assessments (L. Chen et al., 2023; Cubillos & Rienzo, 2023) may improve prediction tools for risk of dementia and need for long-term care.

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