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CARDIOVASCULAR RISK FACTORS SINCE CHILDHOOD AND COGNITIVE PERFORMANCE IN MIDLIFE

The Cardiovascular Risk in Young Finns Study

Juuso Hakala

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ABSTRACT

According to the World Health Organization, dementia and cognitive deficits are major global health and social care challenges in the 21st century. As the population ages, the need for preventive means against cognitive deficits becomes crucial. The risk of cognitive deficits is influenced by e.g., cardiovascular risk factors, which may begin to exert their influence decades before any detectable cognitive symptoms.

This thesis aims to close the existing knowledge gap on the association between the cardiovascular risk factors since childhood and cognitive performance in midlife. The specific aim is to study how 1) physical activity accumulation since childhood; 2) blood pressure, serum lipids, obesity, and their accumulation since childhood; and 3) serum creatinine since adulthood are associated with cognitive performance.

This thesis is a part of the prospective population-based Cardiovascular Risk in Young Finns Study that focuses on cardiovascular risk factors from childhood to adulthood with a follow-up time of over 30 years. The baseline study was conducted in 1980, with 3,596 randomly selected boys and girls aged between three and 18 participating in clinical examinations. The follow-up studies were conducted in three- to nine-year intervals. In the follow-up study conducted in 2011, the cognitive performance of 2,026 subjects aged between 34 and 49 was assessed using computerized cognitive testing.

In this thesis, low physical activity, high blood pressure, elevated total cholesterol and LDL cholesterol, and overweight and obesity since childhood and low serum creatinine since adulthood were observed to be associated with poorer cognitive performance in midlife. Especially, cardiovascular risk factor accumulation (blood pressure, total cholesterol, and obesity) was observed to be associated with poorer cognitive performance in a dose-responsive manner.

If these associations turn out to be causal, the observations can be utilized for aiming to better cognitive health in adulthood by targeting preventive means against cardiovascular risk factors already in childhood and adolescence. Hence, those individuals with a worse cardiovascular risk factor profile since childhood might especially benefit from, for example, adopting healthier lifestyle.

KEYWORDS: Cognitive performance, risk factors, longitudinal study, population study

TURUN YLIOPISTO
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JUUSO HAKALA: Sydän- ja verisuonisairauksien riskitekijät lapsuudesta alkaen ja kognitiivinen toiminta keski-iässä: Lasten Sepelvaltimotaudin Riskitekijät -tutkimus
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TIIVISTELMÄ

Maailman terveysjärjestön WHO:n mukaan kognitiivisen toiminnan heikentyminen on yksi suurimpia sosiaali- ja terveydenhuollon haasteita 2000-luvulla. Ikääntyvän väestön myötä tarve toimille kognitiivisen toiminnan heikentymisen ehkäisemiseksi kasvaa. Kognitiivisen toiminnan heikentymisen riskiin vaikuttavat mm. sydän- ja verisuonisairauksien riskitekijät, jotka saattavat alkaa vaikuttaa jopa vuosikymmeniä ennen havaittavien kognitiivisten oireiden ilmenemistä.

Väitöskirjatutkimuksen tavoitteena on tutkia mahdollisesti jo lapsuudesta alkaen vaikuttavien sydän- ja verisuonisairauksien riskitekijöiden yhteyksiä kognitiiviseen toimintaan keski-iässä. Tavoitteena on selvittää miten lapsuudesta alkaen 1) kertynyt fyysinen aktiivisuus; 2) kohonnut verenpaine, korkeat kolesteroliarvot, ylipaino ja näiden kasautuminen; sekä aikuisuudesta alkaen 3) matala seerumin kreatiniinitaso ovat yhteydessä kognitiiviseen toimintaan keski-iässä.

Väitöskirjatutkimus on osa Lasten Sepelvaltimotaudin Riskitekijät (LASERI) -pitkittäistutkimusta, jossa sydän- ja verisuonisairauksien riskitekijöitä on seurattu yli 30 vuotta. LASERI käynnistyi vuonna 1980, jolloin 3596 3–18-vuotiasta lasta osallistui ensimmäiseen kenttätutkimukseen, minkä jälkeen heitä on seurattu 3–9 vuoden välein. Kognitiivista toimintaa mitattiin vuoden 2011 seurantatutkimuksessa neuropsykologiseen kognitiiviseen testaukseen perustuvalla menetelmällä 2026 tutkimushenkilöltä, jotka olivat tuolloin iältään 34–49 vuotta.

Kohonnut verenpaine, korkeat kokonais- ja LDL-kolesteroli, ylipaino sekä vähäinen fyysinen aktiivisuus jo lapsuudesta alkaen sekä matala seerumin kreatiniini aikuisuudesta alkaen olivat yhteydessä heikompaan keski-iän kognitiiviseen toimintaan. Erityisesti lapsuudesta alkava riskitekijöiden kasautuminen (verenpaine, kokonaiskolesteroli, ylipaino) voimisti tätä yhteyttä.

Jos taustalla on syy-seuraussuhde, voidaan löydöksiä hyödyntää kohdistamalla ennaltaehkäiseviä toimia sydän- ja verisuonisairauksien riskitekijöihin aikaisempaa aktiivisemmin lapsiin ja nuoriin pyrittäessä parantamaan kognitiivista terveyttä aikuisuudessa. Tällöin henkilöt, joilla on huono riskitekijäprofiili lapsuudesta alkaen, voisivat erityisesti hyötyä esimerkiksi terveiden elintapojen omaksumisesta.

AVAINSANAT: Kognitiivinen toiminta, riskitekijät, pitkittäistutkimus, väestötutkimus

Table of Contents

Abbreviations

AHA	American Heart Association
APOE	Apolipoprotein E
ARIC	Atherosclerosis Risk in Communities
AUC	Area under the curve
BIC	Bayesian Information Criterion
BMI	Body mass index
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CANTAB®	Cambridge Neuropsychological Test Automated Battery
CARDIA	Coronary Artery Risk Development in Young Adults
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
DBP	Diastolic blood pressure
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
PA	Physical activity
PAI	Physical activity index
PAL	Paired Associates Learning test
RTI	Reaction Time test
RVP	Rapid Visual Information Processing test
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
SWM	Spatial Working Memory test
WHO	World Health Organization
Young Finns Study	Cardiovascular Risk in Young Finns Study

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 Hakala JO, Rovio SP, Pahkala K, Nevalainen J, Juonala M, Hutri-Kähönen N, Heinonen OJ, Hirvensalo M, Telama R, Viikari JSA, Tammelin TH, Raitakari OT. Physical Activity from Childhood to Adulthood and Cognitive Performance in Midlife. *Medicine and Science in Sports and Exercise* 2019; 51: 882–890.

II Hakala JO, Pahkala K, Juonala M, Salo P, Kähönen M, Hutri-Kähönen N, Lehtimäki T, Laitinen TP, Jokinen E, Taittonen L, Tossavainen P, Viikari JSA, Raitakari OT, Rovio SP. Cardiovascular Risk Factor Trajectories Since Childhood and Cognitive Performance in Midlife: The Cardiovascular Risk in Young Finns Study. *Circulation 2021*; 143: 1949–1961

III Hakala JO, Pahkala K, Juonala M, Salo P, Kähönen M, Hutri-Kähönen N, Lehtimäki T, Laitinen TP, Jokinen E, Taittonen L, Tossavainen P, Viikari JSA, Raitakari OT, Rovio SP. Repeatedly Measured Serum Creatinine and Cognitive Performance in Midlife: The Cardiovascular Risk in Young Finns Study. *Neurology 2022*; 98: e2268-e2281

1 Introduction

Dementia is one of the greatest global health and social care challenges in the 21st century [1]. With an aging population, the prevalence of cognitive deficits is increasing worldwide [2]. By 2050, 152 million people will be demented, and several more will have milder cognitive deficits [3]. Alzheimer's disease is the most common cause of dementia [4]. Delaying the onset of Alzheimer's disease by one year is estimated to reduce its total worldwide number of cases in people over 60 in 2050 by 11% [5]. Several subclinical cognitive deficiencies—memory skills, learning, decision making, and problem solving—precede dementia years or even decades before they become clinically detectable [4]. The origin of cognitive deficits and dementias is multifactorial: for example, lifestyle, genetic predisposition, cardiovascular risk factors, and environmental factors influence cognitive performance [3]. Simultaneously, the prevalence of unfavorable lifestyle habits, such as physical inactivity, has remained high in the 21st century [6]. Such habits are known to result in negative premises for cognitive and overall health, such as increasing the need for health care and increasing the social and economic burden on society [4]. Reducing the prevalence of risk factors for cognitive deficits is thus a crucial target on the global public health agenda [3].

In its recent statement in 2020, the Lancet Commission on Dementia Prevention, Intervention, and Care proposed that 12 potentially modifiable risk factors account for around 40% of cognitive deficits and dementia worldwide [3]. These risk factors are divided into early life, midlife, and later life risk factors (Figure 1). However, as observed in many previous studies, several cardiovascular risk factors might start to influence cognitive performance earlier than believed. For example, physical activity—which the Lancet Commission's statement defined as a later life risk factor for cognitive deficits and dementia—may influence cognitive performance from young adulthood [7].

Most of the previous studies that have examined the association between different risk factors and cognitive performance are often limited in their focus on the association of a single risk factor. However, adverse cardiovascular risk factors often tend to accumulate. The number of studies that have examined the association between cardiovascular risk factor accumulation since childhood and later life

cognitive performance is scarce. Furthermore, most of the previous studies have not assessed risk factors longitudinally, which restrains them from evaluating the plausible effect exposure time or, on the other hand, the critical age windows for adverse risk factors. Moreover, in the Lancet Commission's statement, 60% of the risk factors influencing the prevalence of dementia remain unknown. In addition to the 12 potentially modifiable risk factors presented in the statement, previous literature has suggested the existence of other modifiable risk factors as well, such as adverse serum lipids, chronic kidney disease, and low serum creatinine.

This thesis aims to identify the associations of cardiovascular risk factors since childhood, and especially their longitudinal exposure and accumulation until midlife, with cognitive performance, which is assessed in midlife in the unique population-based cohort of the Cardiovascular Risk in Young Finns Study (Young Finns Study). Launched in 1980, the Young Finns Study clinically examined 3,596 boys and girls between three and 18 years old. The initial purpose of the study was to examine the role of cardiovascular risk factors and lifestyle factors already since childhood in leading to cardiovascular diseases. The clinical examinations were conducted repeatedly in three- to nine-year intervals. After 31 years of follow-up in early midlife, the cognitive performance of the participants was assessed using a computerized neuropsychological test. This prospective cohort enables the examination of the roles of early life risk factors and longitudinal risk factor accumulation in adulthood cognitive health.

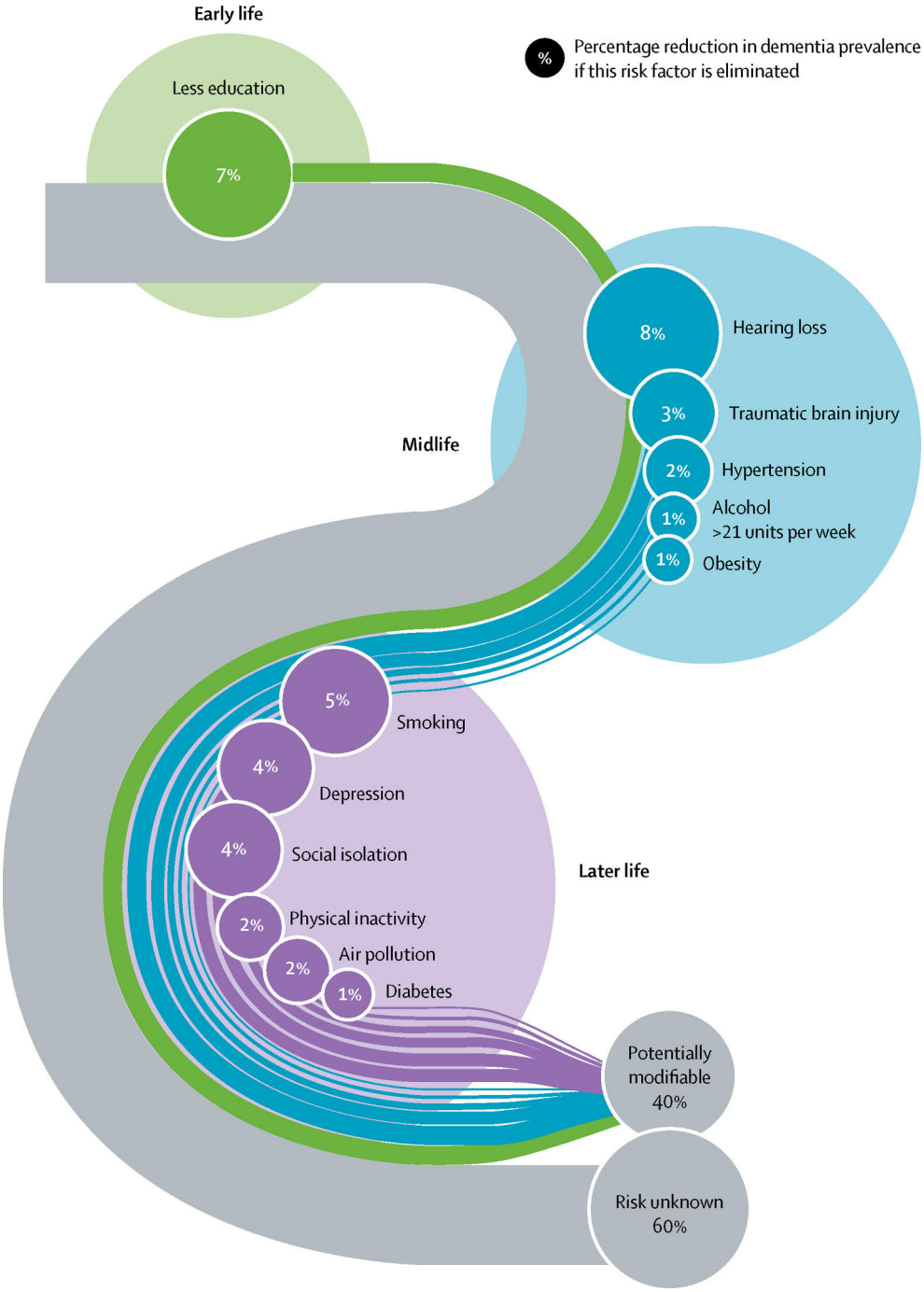

Figure 1. Population attributable fraction of potentially modifiable risk factors for dementia. The figure has been reused from the work of Livingston et. al., 2020; Dementia prevention, intervention, and care: 2020 report of the Lancet Commission [3] with permission of Elsevier.

2 Review of the Literature

2.1 Cognition and cognitive aging

2.1.1 Cognition

Cognition—cognitive performance or cognitive function—is a complex system of brain functions that refers to an individual's mental processes involved in knowledge acquisition, information processing, and reasoning [8]. Cognitive functions are divided into cognitive domains, such as memory, learning, executive functions, visuospatial abilities (e.g., face-object recognition), and language abilities [8]. These cognitive domains are further categorized into subgroups with a specific part of brain function. Memory is categorized as declarative (explicit) and nondeclarative (implicit or nonconscious) memory [9]. Declarative memory is divided into episodic memory and semantic memory, the former including the memory of personal events, the latter the memory of general facts [10]. Executive functions are divided into inhibitory control, working memory, cognitive flexibility, fluid intelligence (i.e., reasoning and problem solving), and planning [11]. The cognitive functions are located in at least five anatomically distinct neural network areas in the brain's cerebral cortex: 1) declarative memory in the hippocampal-entorhinal complex and in the amygdala; 2) executive functions in the lateral prefrontal cortex and, possibly, in the posterior parietal cortex; 3) visuospatial abilities in the mid-temporal and temporal cortices; 4) spatial awareness in the posterior parietal cortex and the frontal eye fields; and 5) language abilities in Wernicke's and Broca's areas [12].

2.1.2 Cognitive deficits

Cognitive function is impaired not only in different types of dementia but also in milder cognitive deficits. The pathophysiological disease process, for example in Alzheimer's disease, is known to begin years or even decades before any clinical symptoms emerge [13]. After they emerge, no cure or even effective medical treatment is available to markedly slow down the disease [13]. Moreover, subclinical deficiencies in memory skills, learning, decision making, and problem solving precede dementia years or decades before they become clinically apparent [4].

2.1.3 Cognitive aging and sex differences in cognitive performance

Increased age is associated with lower levels of cognitive performance. Age-related cognitive decline possibly begins in healthy educated adults when they are already in their 20s and 30s, but the cognitive decline is accelerated at older ages, especially after 60 [14]. Normal age-related cognitive change does not impair a person's ability to perform daily activities [15]. Aging causes structural and neurophysiological changes in the brain, with a variable degree of cognitive decline [16]. The changes occur in brain regions with less coordinated and localized activity, leading to poor performance in several cognitive domains. Some cognitive abilities, such as vocabulary, are resilient to brain aging and may even improve with age [15]. Other abilities, such as processing speed, memory, language, visuospatial functions, and executive functions, decline gradually over time. Age-related brain changes might contribute to the mechanisms in the pathogenesis of neurodegenerative disorders, such as dementias [3].

Furthermore, it is hypothesized that having a higher cognitive reserve—the brain's ability to flexibly and efficiently use cognitive networks (networks of neuron-to-neuron connections) that enables individuals to continue conducting cognitive tasks despite brain changes—may protect against age-related cognitive decline and deficits [13]. For example, having more years of education and social and mental activities (such as a mentally stimulating job) might enhance cognitive reserve. Especially early life factors, such as less education, are suggested to affect the development of the cognitive reserve [3]. This hypothesis is supported by the observations where older women were found to more likely develop dementia than men of the same age, probably partly because, on average, older women have had less education than older men [3]. However, the early life factors that might contribute to cognitive reserve development before the onset of age-related cognitive decline remain uncertain.

The role of sex differences in cognitive performance between men and women as well as between boys and girls has been observed throughout their lifespan [17]. Men usually outperform women in spatial tasks, whereas women outperform men in some memory and verbal tasks [17]. It is important to note that sex differences in cognitive performance are reported as average values, so when comparing these values, individual men or women might excel in a cognitive task where the opposite sex is observed to outperform the other sex.

In the Young Finns Study (the study population of this thesis), similar differences as reported in previous literature were observed in the cognitive performance between men and women in midlife [18]. Men outperformed women in cognitive tests that measured short-term working memory, reaction and movement time, and

visual processing and sustained attention. Women outperformed men in episodic memory and associative learning.

The potential reason for the role of sex difference in cognitive performance is hypothesized to be its link with sex hormones [19]. It is possible that critical brain development periods, such as in utero, shortly after birth, and during puberty, may influence cognitive development [17]. Furthermore, cultural influences, gender stereotypes, and biopsychosocial interactions potentially modify brain development during an individual's lifespan [17]. However, the detailed mechanisms for this modification remain uncertain.

2.1.4 Dementia and mild cognitive impairment

Dementia is a clinical syndrome with variable manifestations that are usually chronic or progressive [1]. Dementia is defined as the chronic, acquired loss of two or more cognitive abilities caused by brain disease or injury [20]. Alzheimer's disease is the most common form of dementia and may contribute to 60–70% of cases. However, approximately 50% of these are estimated to be "pure" Alzheimer's disease, while others are estimated to be different forms of "mixed dementia" [21], where most often Alzheimer's disease and vascular dementia are mixed. After Alzheimer's disease, the most common forms of dementia include vascular dementia, Lewy body disease, and a group of diseases that contribute to frontotemporal dementia [20].

The most common clinical presentation of Alzheimer's disease is a slow onset and gradually progressive loss of memory, typically accompanied by an inability to learn new information and, particularly, autobiographical information, such as recent events in one's life. This is because Alzheimer's disease preferentially affects the brain networks involved in episodic memory [20]. In vascular dementia, impaired judgment or impaired ability to make decisions, plan, or organize may be the initial symptom, but memory may also be affected, especially when the brain changes associated with other causes of dementia are present [13]. Motor difficulties, such as slow gait and poor balance, may also exist.

Dementia with Lewy bodies is characterized by a chronic rapid eye movement behavior disorder with early visuospatial impairment [20]. Frontotemporal dementia is characterized by a behavioral variant (the most common presentation is disinhibition) or, less often, a language impairment variant (such as semantic dementia, where the meaning of the patient's speech is unclear) [20].

Mild cognitive impairment (MCI) is defined as performance that is lower than normal on objective neuropsychological cognition tests. However, they are still capable of engaging in daily functions (i.e., they still have the ability to function in society—such as behave and engage as required at work, home, and in social settings—and engage in daily activities, such as taking care of themselves). MCI is

thus not consistent with dementia [20]. MCI does not always progress into dementia, and a patient's cognitive status may become normal or fluctuate between MCI and normal cognition [20].

2.2 Mechanisms for cognitive decline

2.2.1 Neuropathology in dementias

Functional magnetic resonance imaging (MRI) studies suggest that changes in the activity of the hippocampus and associated cortical regions can distinguish normal aging from pathological aging [16]. In normal aging, metabolic activity is reduced in the subiculum and the dentate gyrus, whereas in pathological ageing, the metabolic activity in the entorhinal cortex is reduced as a possible early change in Alzheimer's disease [16]. There are several possible changes in brain function that are associated with different types of dementia.

In the early stages of Alzheimer's disease, brain atrophy is located especially in the medial temporal lobe, including the hippocampus. The characteristic pathological processes are accumulation of beta-amyloid plaques outside neurons and abnormal form of the protein tau inside neurons that may contribute to the damage and death of neurons by interfering with neuron-to-neuron communication at synapses or blocking the transport of nutrients and other essential molecules inside neurons [13].

In vascular dementia, brain tissue damage is caused by small lacunar infarcts, multiple microinfarcts, or large infarcts, including intracerebral hemorrhage. The characteristic pathological process includes blood vessel damage, such as atherosclerosis and arteriolosclerosis [20]. In dementia with Lewy bodies, brain atrophy is associated with the intraneuronal accumulation of abnormal aggregations of the protein alpha-synuclein in the brain's neocortex [20]. In frontotemporal dementia, focal brain atrophy is located in the frontal and/or anterior temporal lobes [20].

2.2.2 Molecular pathogenesis in age-related cognitive decline

The development of age-related cognitive decline occurs during a series of pathophysiological changes in cerebral microvascular regulation [22]. Cerebral blood flow is regulated by a complex system. The potential consequences of age-related cerebral blood flow dysregulation include blood–brain barrier disruption, neuroinflammation, neurodegeneration exacerbation, cerebral microhemorrhage development, microvascular rarefaction, and ischemic neuronal dysfunction and

damage. Local vasoregulatory mechanisms possibly underlie these consequences, such as myogenic autoregulation, endothelium-dependent pathways, and neurovascular coupling. Even mild impairment of cerebral blood flow regulation may have significant consequences for cognitive performance. Moreover, an aged brain may be more susceptible to the damaging effects of comorbid conditions, such as hypertension and obesity [22.]

Myogenic autoregulation

Autoregulation maintains the cerebral blood flow relatively constant despite perfusion pressure changes due to systemic blood pressure variability [22]. The adaptation to blood pressure variability is ensured by the pressure-induced myogenic constriction of the cerebral arteries, where vascular resistance is rapidly adjusted. Hence, increased resistance in the proximal arteries assures that increased arterial pressure does not penetrate the distal microcirculation and damage the brain's thin-walled arteriolar and capillary microvessels. Functional adaptation to high blood pressure is extended to a wider range in young individuals. Age-related changes in cerebral arteries thus impair the adaptive increase in myogenic constriction, leading to cerebrovascular autoregulatory dysfunction [22.]

Eventually, age-related changes lead to an increased hemodynamic burden in the cerebral blood flow, exacerbating the disruption of the blood–brain barrier, leading to the extravasation of plasma factors [22]. This might promote neuroinflammation, e.g., activation of microglia by IgG via the IgG Fc receptors. The microglia-derived proinflammatory cytokines, chemokines, proteases (i.e., matrix metalloproteinase), and reactive oxygen species promote neuronal damage. In addition, the increased microvascular pressure is suggested to activate matrix metalloproteinases in the vascular wall in a redox-sensitive manner, which could contribute to the development of microhemorrhages. Age-related autoregulatory dysfunction and its consequences may also contribute to the dysfunction of the glymphatic system and the development of age-related vascular rarefaction. These damages in the brain are hypothesized to be linked to risk factors—such as elevated blood pressure—and cognitive impairment in aging and to especially increase the prevalence of Alzheimer's disease [22.]

Endothelium-dependent pathways

The vascular endothelium of the cerebral vessels produces vasoactive substances, such as nitric oxide, eicosanoid mediators, endothelium-derived hyperpolarizing factors, and endothelins, all of which are involved in regulating cerebral blood flow. Nitric oxide, in particular, plays a major role. With age, nitric oxide generation

capacity in the vascular endothelium is reduced, leading to endothelial dysfunction and, thereby, circulatory impairment in the brain and heart [22.]

The endothelial nitrous oxide synthase produces nitrous oxide, which causes vasodilation, an increase in blood flow, a decrease in vascular resistance, hypotension, inhibition of platelet aggregation and adhesion, and a decrease in vascular smooth muscle cell proliferation. The nitrous oxide-dependent pathways also protect endothelial cells from apoptosis, have an antioxidative role, and exert anti-inflammatory and proangiogenic effects [22.]

In aging, the production of reactive oxygen species in mitochondria is increased, causing oxidative stress in the vascular smooth muscle cells [22]. In experimental animal models, both reactive oxygen species generation and endothelial dysfunction are involved in cerebral hypoperfusion and are possible trigger factors in age-related cognitive decline and in developing Alzheimer's disease [23]. It is important to note that comorbid conditions, e.g., high blood pressure and metabolic diseases, exacerbate aging-induced endothelial dysfunction [23].

Neurovascular coupling

In neurovascular coupling, high energy demand of neurons during neuronal activity is rapidly fulfilled by the cerebral blood flow's regional functional hyperemia. This response is a result of the coordinated interaction of neurons, astrocytes, endothelial cells, and the smooth muscle cells of cerebral arterioles. Aging impairs this neurovascular coupling response through complex changes, where the decreased concentration of circulating insulin-like growth factor-1 leads to impaired astrocyte function and an endothelium-mediated mechanism in functional hyperemia. Impaired astrocyte function is related to the decreased production of vasodilators, including nitrous oxide, and the impaired release of adenosine triphosphate. Both mechanisms increase the production of reactive oxygen species in mitochondria and astrocytes. In impaired neurovascular coupling, the attenuated increase in cerebral blood flow to neuronal activation disrupts the energy metabolism in the cerebral tissue, thus accelerating cognitive decline [22.]

2.3 Measures of cognition

2.3.1 Traditional measures of cognitive performance

Cognitive examination identifies the presence, severity, and nature of cognitive impairment (e.g., memory vs. language) and considers cultural, linguistic, educational, and other factors, such as anxiety and sleep deprivation [20]. Cognitive performance can be assessed using various traditional 'paper and pencil' tests.

Numerous tests are widely used in population-based cohort studies. For example, executive functions are assessed using tests such as the Wisconsin Card Sorting Test, Phonemic Verbal Fluency, Stroop ColorWord Interference Test, and Digit-Symbol Substitution Test [24]. To assess the memory function, for example, the Rey Auditory Verbal Learning Test, immediate and delayed (i.e., 5 to 30 min) recall, and word list learning (i.e., 10 to 20 words) are used. As these non-computerized cognitive tests have a longer history compared to computerized tests, the longitudinal association between the tests and cognitive deficits has been studied. For example, compared to those with better baseline performance, poorer baseline performance in the Rey Auditory Verbal Learning Test has been shown to be longitudinally associated with cognitive decline and progression to dementia [25].

Traditional cognitive tests also include screening tools for assessing impaired cognitive performance in clinical practice. A commonly used tool is the Montreal Cognitive Assessment [26], which requires about 10 minutes to administer and is useful for the early detection of cognitive impairment, including MCI with executive dysfunction. It is commonly used in clinical practice and less used in population-based studies to study the roles of different risk factors in cognitive performance. Another commonly used tool for screening cognitive performance is the Mini-Mental State Examination (MMSE) [27], which was developed more than four decades ago. It is less sensitive to the presence of MCI and less thoroughly evaluates the domains of executive function, higher level language skills, and complex visuospatial processing [20]. It is a common tool in clinical practice and is also used in some studies that examined the associations between different risk factors and cognitive performance. In addition, the Consortium to Establish a Registry for Alzheimer's disease (CERAD) neuropsychological battery includes the MMSE and a 10-item word list learning, a verbal fluency test, a 15-item Boston naming test, a recall and recognition test, and a constructional praxis and recall test [28]. In Finland, the CERAD neuropsychological battery is commonly used in dementia screening.

2.3.2 Computerized testing of cognitive performance

During the last 10 years, cognitive assessment using computerized tests has become more common, though traditional 'paper and pencil' tests have been more frequently used in population-based studies and clinical practice [29]. Although neuropsychological cognitive testing in clinical practice is widely used to diagnose dementias [13], the degree of using computerized tests in neuropsychological testing in clinical practice is unknown. Computerized tests can offer more efficient and accurate assessments of cognitive performance than the existing traditional tests. Their key advantages are time and cost savings, absence of examiner bias, and the way in which the tasks are scored and interpreted by comparing individual test scores

objectively within the context of thousands of normative data points [29]. Importantly, computerized cognitive testing might offer a possibility for the earlier diagnosis of cognitive deficits [30].

There are several different computerized test batteries to assess cognitive performance. A review by Zygouris et al. (2015) identified 17 test batteries [30], and another review by Wild et al. (2008) identified 18 test batteries, out of which 11 were appropriate for cognitive testing in the elderly [31]. For example, the Cambridge Neuropsychological Test Automated Battery (CANTAB®) is currently one of the most widely used computerized test batteries in scientific publications with reports on normative data, test–retest reliability, and clinical use [30]. Originally, CANTAB® was standardized on a large, predominantly elderly population [32]. Today, it is also used to evaluate, for example, cognition in five-to-11-year-old normal, learning-disabled, and autistic children. The battery has been shown to be sensitive in differentiating healthy controls [33], patients with early-stage Alzheimer's disease [34], and patients with Parkinson's disease [30]. For example, each cognitive test performed using the CANTAB® battery in patients with Alzheimer's disease has been observed to be associated with poorer performance than patients with MCI [35]. However, since no longitudinal associations for the risk of dementia have been studied, there exists a gap of knowledge in the CANTAB® as well as in other computerized test batteries.

2.4 Risk factors for cognitive performance, cognitive decline, and dementia

The greatest risk factors for cognitive deficits and dementias, such as Alzheimer's disease, are old age, genetics, and having a family history of Alzheimer's disease [13]. According to the Lancet Commission's recent statement, hypertension, alcohol consumption of ≥21 units per week, obesity, traumatic brain injury, and hearing loss in midlife are associated with increased risk of dementia [3]. Smoking, depression, physical inactivity, social isolation, air pollution, and diabetes in later life are also risk factors for dementia. By far, the only risk factor acknowledged as an early life risk factor for dementia is low education. In the Lancet Commission's statement, these potentially modifiable risk factors are estimated to reduce the prevalence of dementia by 40% if all the factors are eliminated [3]. Still, several risk factors of dementia and the most effective age windows for preventive means remain undetermined, highlighting the need to identify the potential risk factors and, especially, the risk factors from early life and beyond to reduce the global burden of cognitive deficits. It is thus paramount to extensively examine genetic predisposition, environmental factors, cardiovascular risk factors, multiple risk factor accumulation, and lifestyle risk factors in relation to life-course cognitive performance.

2.4.1 Genetics

The apolipoprotein E (APOE) ε4 allele is the only certain genetic factor that significantly increases susceptibility to late-onset Alzheimer's disease (the onset age older than 65 years) [36]. The other APOE alleles are ε3 and ε2. ε3 homozygotes are the most common genotype, having a frequency of over 50% in the American population [13]. Compared with APOE ε3 homozygotes, APOE ε4 heterozygotes have a three times and homozygotes 15 times higher risk of Alzheimer's disease, respectively. For routine dementia evaluation, APOE genotype assessment is not recommended, as currently medical management would not be altered by the test results [20]. It has been reported that, in the American population, 2.4% were APOE ε4 homozygotes and 23.8% APOE ε4 heterozygotes [13], while in Finnish population (Young Finns Study population), the prevalence is higher: 3.2% were APOE ε4 homozygotes and 30.6% were APOE ε4 heterozygotes [37].

The presence of APOE ε4 has been associated with increased disturbances in several biochemical changes that are characteristics of Alzheimer's disease, such as beta-amyloid deposition, tau formation, neurodegeneration, lipid dysfunction, loss of synaptic plasticity, cholinergic dysfunction, and disruption of signaling [38]. For example, APOE ε4 is shown to lead to accelerated breakdown of the blood–brain barrier, which is an early biomarker of cognitive dysfunction [39]. APOE ε4 also causes the degeneration of brain capillary pericytes that maintain the blood–brain barrier integrity. The breakdown of the blood–brain barrier in APOE ε4 carriers is especially seen in the hippocampus and medial temporal lobe [39]. In addition to APOE genotypes, some specific mutations are identified in several genes, thus increasing the risk of Alzheimer's disease and frontotemporal dementia [36]. However, these mutations are rare and not typically assessed in clinical practice, except in early-onset dementias.

2.4.2 Environmental factors

Several environmental factors—socioeconomic status (SES), low education, and childhood school performance—are associated with cognitive performance and the risk of dementia [3]. SES is a construct that broadly represents an individual's or family's ranking or accumulated capital within a cultural system of social class [40]. SES measurement is complex, as several indicators are used for it, the most common of them being income, occupation, and education, or some combination of them [41]. Childhood SES, determined by the SES of parents or caregivers, may affect children's development independent of the achieved adulthood SES [41]. Parental income, occupation, and education are thus typically used to assess childhood SES.

In several previous studies, high childhood SES was found to be associated with better cognitive performance later in life [42–45]. Furthermore, some studies have

suggested an association between higher childhood SES and slower age-related cognitive decline [44], while some studies have not observed any association between SES and cognitive decline [42,43,45]. Moreover, higher childhood SES is related to a reduced risk of dementia [46]. The detailed mechanisms for high childhood SES and later life cognitive performance are uncertain. Higher childhood SES may have an effect on brain development, where cognitive stimulation, nutrition, parenting styles, or physical environment might play a role [41]. Higher SES may offer health benefits, including improved living and working conditions, access to health services, and differences in lifestyle and behavior.

Low education is an indicator of low life-course SES. It is acknowledged by the Lancet Commission as the only early life risk factor for the increased risk of dementia in late life [3]. There is sufficient evidence that people with higher education perform better across a broad range of cognitive tasks [47]. Despite this, high education was found to be associated with better cognitive performance; a recent review and meta-analysis observed no association between high educational attainment and a decline in cognitive performance in the general population [48]. This may indicate that having a high level of education does not shield individuals from age-related cognitive decline. In addition, in the Young Finns Study (the study population of this thesis), higher education was previously observed to be associated with better performance in all cognitive domains in midlife [18]. There are several potential mechanisms behind higher education and better cognitive performance. Education has been suggested to directly increase cognitive performance at a younger age and, possibly, alter how cognitive tasks are processed [47]. It is thus possible that people with higher education, since they have more cognitive reserve compared to less educated individuals, can tolerate more cognitive decline.

Furthermore, childhood cognitive ability is a strong predictor of cognitive performance later in life [49]. For example, in the 1946 British birth cohort study with 2,058 individuals, better results in cognitive ability and reading comprehension tests at the age of 15 were found to be associated with less decline in memory and search speed measured between the ages of 43 and 53 [50]. Moreover, better childhood school performance was found to be associated with better cognitive performance and reduced cognitive decline [51]. These factors might contribute to the development of a better cognitive reserve, one that may protect and postpone the onset of cognitive decline and dementia. Higher cognitive ability in childhood also likely leads to more favorable life circumstances in adulthood, higher educational attainment, and higher SES [51].

2.4.3 Cardiovascular risk factors

The incidence of cognitive deficits is influenced by well-established cardiovascular risk factors, such as elevated blood pressure, adverse serum lipids, obesity and overweight, diabetes, and cardiovascular risk factor accumulation [3]. The development of dementia is hypothesized to be preceded by changes in the risk factor levels, where first the body mass index (BMI) and then the blood pressure rises between childhood and midlife and then falls more steeply in those who develop dementia [52]. Before the dementia diagnosis, weight is hypothesized to fall around 10 years, and blood pressure around five years [52].

For each cardiovascular risk factor, specific clinical guideline cutoff levels have been developed to indicate the risk of cardiovascular disease or stroke. Clinical guidelines are published by different organizations, such as the World Health Organization (WHO), the American Heart Association (AHA), or the Current Care Guidelines (in Finland). Depending on the organization, there are some minor differences between the cutoff levels, but for the most part, the guidelines are similar. In addition to cardiovascular diseases, an increasing amount of evidence indicates that cardiovascular disease guideline cutoffs might be applicable to cognitive deficit prevention as well.

The association between cardiovascular risk factors and cognitive performance or the risk of dementia has usually been studied by examining the association of a single risk factor. This highlights the need for future studies to consider risk factor accumulation in more detail. Furthermore, observational studies have usually used age, sex, ethnic background (if needed), and some SES indicators—such as education, income, or occupation—to control the confounders for the associations between the studied risk factor and the outcome, i.e., cognitive performance or the risk of dementia. Moreover, other covariates are also used variably to control the association, such as blood pressure, serum lipids, BMI, diabetes, smoking, physical activity, alcohol consumption, cardiovascular diseases, and depression. In addition, most of the previous observational studies on risk factors for cognitive performance were focused on late life or middle age, while only a few studies exist that focused on adulthood. Cohort studies that applied a life-course perspective from childhood to old age do not exist and, therefore, the association between childhood and adulthood cardiovascular risk factors and cognitive performance or the risk of dementia in late life remains obscure.

One study with pooled data from four prospective cohort studies (the Coronary Artery Risk Development in Young Adults (CARDIA) study, the Multi-Ethnic Study of Atherosclerosis, the Cardiovascular Health Study, and the Health, Aging and Body Composition study) assessed the association between early life risk factors and cognitive performance in late life using the imputation method for the risk factors [53]. In this study, 15,001 participants' (age range 18 to 95 years) cognitive

performance was assessed repeatedly at different ages. The cohort was synthetic, where participants from the CARDIA study were youngest (age range 18 to 30 years at baseline) compared to the other three cohorts, where the participants were older (age range 45 to 100 years at baseline). For the cohorts with older participants, the cardiovascular risk factor levels earlier in life were estimated by imputing the data on BMI, fasting glucose, systolic blood pressure, and total cholesterol. Imputed elevated BMI, fasting glucose, and systolic blood pressure were observed to be associated with greater later life cognitive decline. Especially, the association between early adulthood adverse cardiovascular risk factor levels and cognitive decline was pronounced, suggesting an important role of early life cardiovascular risk factor levels in later life cognitive health. However, no association between total cholesterol and cognitive performance was observed, and cardiovascular risk factor accumulation was not examined. All the associations were adjusted for age, sex, ethnic background, education, cohort, and different age windows for each cardiovascular risk factor exposure.

It is important to note that cardiovascular risk factor level imputation offers a possible source of bias, where early and midlife exposures might point toward average levels that might attenuate their associations with cognitive decline [53]. Nevertheless, the early life adverse risk factors might have an important role in late life cognitive performance. To clarify these associations, prospective studies with follow-up time extending throughout decades are needed.

2.4.3.1 Elevated blood pressure

In clinical guidelines, hypertension is defined by the AHA as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg [54]. In AHA's Life's Simple 7 ideal cardiovascular health metrics, systolic/diastolic blood pressure at the level <120 mmHg / <80 mmHg is considered to indicate ideal, 120 to 139 mmHg / 80 to 89 mmHg or treated to goal is considered to indicate intermediate, and ≥140 mmHg / ≥90 mmHg is considered to indicate poor cardiovascular health [54]. These guideline-level cutoffs were initially developed to reduce the risk of cardiovascular disease and stroke, but recent evidence indicates that these guideline levels might be useful for cognitive health as well.

Midlife hypertension is acknowledged by the Lancet Commission as a risk factor for dementia [3]. Some studies also indicate that low blood pressure in old age is associated with worse cognitive performance. In a study with 1,449 participants from the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study, high systolic blood pressure (≥160 mmHg) in midlife was associated with a higher risk of Alzheimer's disease after an average of 21 years of follow-up compared to those with normal systolic blood pressure in midlife [55]. In another report from the

Atherosclerosis Risk in Communities (ARIC) study, 5,995 participants (with a mean age of 57 years at baseline) were followed up for 20 to 25 years [56]. Hypertension in late midlife was associated with an increased risk of late life MCI and dementia. Additionally, in a cohort study on members of the Kaiser Permanente Medical Care Program of Northern California, the cardiovascular risk factors were measured in 8,845 participants in midlife between the ages of 40 and 44 and followed up for an average of 26.7 years [57]. Hypertension in midlife was observed to be associated with an increased risk of dementia.

In previous studies with middle-aged or older participants at baseline, high systolic blood pressure was related to worse cognitive performance in later life. In the Tromsø study, the cardiovascular risk factors of 5,033 participants (with a mean age of 58 years) were measured at baseline, and their cognitive performance was assessed after seven years of follow-up [58]. Leveraging these data, higher systolic blood pressure in midlife was associated with worse verbal memory among men and worse processing speed among women. Another report is from the ARIC study, where 13,476 participants aged between 48 and 67 years at baseline were followed up for 20 years, and their cognitive performance was assessed at baseline and after the 20-year follow-up [59]. Compared to those with no hypertension, the study found an association for those with midlife hypertension and steeper cognitive decline; no association for late life systolic blood pressure was observed. Furthermore, in a cohort of older-aged participants in the Framingham Heart Study, 1,423 participants (with a mean age of 66 years at baseline) were followed up for 18 years, and their cardiovascular risk factors were measured repeatedly every two years [60]. Among men, hypertension was found to be inversely associated with learning and memory.

Only a few observational studies have been conducted with younger participants at the baseline. In the CARDIA study, 3,381 participants aged 25 years (ranging from 18 to 30 years) at baseline were followed up for 25 years [61]. Greater cumulative exposure to higher systolic and diastolic blood pressure, especially to levels above the recommended guidelines, was inversely associated with worse cognitive performance in executive function, processing speed, and verbal memory. Furthermore, in a study from the Vieillissement Santé Travail cohort, 3,201 participants aged 32, 42, 52, and 62 years (mean 45 years at baseline) were followed up for 10 years [62]. Hypertension was observed to be associated with poorer global cognition, memory, and processing speed. Furthermore, subjects with untreated and uncontrolled hypertension had poorer cognitive performance compared to those with controlled and no hypertension. In addition, a systematic review and meta-analysis of cross-sectional and prospective studies on individuals from adulthood to old age concluded that hypertension is associated with poorer cognitive performance [63]. Moreover, in the Young Finns Study (the study population of this thesis), systolic blood pressure levels exceeding the recommended guidelines in childhood were

observed to be associated with worse episodic memory and associative learning in midlife [64].

In addition, some previous studies have examined the association between elevated blood pressure levels and cognitive performance in childhood. In a cross-sectional study from the Third National Health and Nutrition Examination Survey with 5,077 adolescents and children (with a mean age of 11.5 years), elevated systolic blood pressure was found to be associated with poorer verbal attention and working memory [65]. In another cross-sectional report from the Generation R Study with 5,644 children (with a mean age of 6.2 years), elevated diastolic blood pressure was found to be associated with nonverbal intelligence [66]. Furthermore, some studies conducted in smaller cohorts reported that elevated blood pressure is associated with worse cognitive performance in children [67].

Concluding, according to the previous literature, there exists evidence for an association between elevated blood pressure in midlife and poor cognitive performance. However, some studies have demonstrated that elevated blood pressure might influence cognitive performance already in early life. It is important to note that the Young Finns Study is by far the only population-based study that highlights the association between elevated blood pressure in childhood and worse cognitive performance in midlife. Previous studies have suggested that elevated blood pressure in childhood is associated with worse cognitive performance in childhood. Therefore, additional evidence is needed on the longitudinal association between blood pressure and cognitive performance over an entire lifespan.

2.4.3.2 Adverse serum lipids

Cholesterol is one of the primary causal risk factors for the development of atherosclerosis and cardiovascular diseases [54]. According to the AHA-defined clinical guidelines for adults, the optimal level of serum total cholesterol is ≤3.8 mmol/l and ≤2.6 mmol/l for low-density lipoprotein (LDL) cholesterol [68]. In AHA's Life's Simple 7 ideal cardiovascular health metrics, a serum total cholesterol level of <5.172 mmol/l is considered to indicate ideal, 5.172 to 6.18 mmol/l intermediate, and >6.18 mmol/l poor cardiovascular health [54]. Furthermore, triglycerides <1.7 mmol/l, HDL cholesterol <1 mmol/l in men and <1.2 mmol/l in women are considered to indicate poor lipid levels [54]. In addition to cardiovascular diseases, adverse serum lipids have been linked to an increased risk of dementia and poorer cognitive performance. Prior evidence has mainly focused on total cholesterol levels; however, the association of LDL cholesterol, HDL cholesterol, and triglycerides with the risk of dementia and cognitive performance is scarce.

Several studies from middle-aged cohorts have examined the association between total cholesterol and the risk of dementia. In the CAIDE study, 1,449

participants were followed up for an average of 21 years [55]. Higher total cholesterol (≥6.5 mmol/l) in midlife was found to be associated with a higher risk of Alzheimer's disease compared to those with lower total cholesterol (<6 mmol/l). In the ARIC study, 5,995 participants (with a mean age of 57 years) were followed up for 20 to 25 years, and hypercholesterolemia in late midlife was found to be associated with an increased risk of late life MCI and dementia [56]. In another report from the cohort study on the members of the Kaiser Permanente Medical Care Program of Northern California, cardiovascular risk factors were measured in 8,845 participants in midlife between the ages of 40 and 44, and they were followed up for an average of 26.7 years [57]. High cholesterol in midlife was found to be associated with an increased risk of dementia. Finally, a systematic review and meta-analysis of prospective studies with total 14,331 participants found that high midlife total cholesterol is associated with an increased risk of dementia later in life, whereas high total cholesterol in old age is not associated with risk of dementia in old age [69]. However, this meta-analysis did not find any association between total cholesterol and vascular dementia.

Several studies have examined the association between total cholesterol and cognitive performance among middle-aged or older participants at baseline. In the Framingham Heart Study, 1,894 participants' cholesterol levels were measured biennially during 16 to 18 years of follow-up, and their cognitive performance was assessed four to six years after the follow-up at a mean age of 67 years [70]. Higher total cholesterol levels in midlife were observed to be associated with poorer verbal fluency, attention, concentration, abstract reasoning, and global cognitive performance. In another study conducted on the ARIC cohort, 13,997 participants with a mean age of 58 years (ranging between 46 and 70 years) were followed up for 20 years, and their cognitive performance was assessed thrice during the follow-up [71]. High total cholesterol, LDL cholesterol, and triglycerides were found to be associated with a greater decline in executive function, sustained attention, processing speed, memory, and global cognitive performance.

Two other cohort studies were also conducted on younger participants. In the Baltimore Longitudinal Study of Aging study, the total cholesterol and cognitive performance were assessed repeatedly (mean 3.2 times) in 1,601 participants aged 19 to 93 years during an average of 6.4 years of follow-up (maximum follow-up 19 years) [72]. A nonlinear association was observed, where higher total cholesterol levels were associated with cognitive decline in all age groups but especially in the middle-aged and young-old groups. However, among the oldest participants, lower total cholesterol levels were found to be associated with accelerated cognitive decline. The cognitive domains that were observed to have accelerated decline were global mental status, verbal learning, executive function, and language. Another report concerning younger participants is from the CARDIA study, where 3,381

participants aged 25 years (range 18 to 30 years) at baseline were followed up for 25 years [61]. Greater cumulative exposure to higher total cholesterol, especially levels above the recommended guidelines, was observed to be associated with worse verbal memory. Moreover, in the Young Finns Study (the study population of this thesis), participants with LDL cholesterol levels exceeding the recommended guidelines in childhood were found to have worse episodic memory and associative learning in midlife than those participants in the lowest LDL cholesterol quartile in childhood [64].

In conclusion, there is sufficient evidence that elevated serum cholesterol levels in midlife are associated with worse cognitive performance and increased risk of dementia. It is important to note that an increasing number of studies indicate that adverse early life lipids may contribute to worse cognitive performance later in life. However, adverse serum lipids in early life have not been linked to early life cognitive performance. In a cross-sectional report from the Third National Health and Nutrition Survey with 4,248 children and adolescents aged between six and 16, no association between adverse serum lipids and worse cognitive or academic performance was observed [73]. This may indicate that this association might become apparent in adulthood or midlife.

2.4.3.3 Obesity and overweight

BMI is typically used to assess obesity and overweight. BMI <25 kg/m^2 is considered to indicate normal weight, BMI 25-29.9 kg/m^2 overweight, and BMI ≥30 kg/m^2 obesity [54]. Midlife obesity is acknowledged by the Lancet Commission as a risk factor for dementia [3]. However, prior evidence on the association between obesity, overweight and cognitive performance is contradictory. Though most of the studies found overweight in midlife to be related to worse cognitive performance or an increased risk of dementia, some studies did not. Furthermore, according to prior evidence, being underweight (BMI <20 kg/m^2) might be associated with poor cognitive performance and increased risk of dementia. Additionally, it has been suggested that weight starts to decline up to 10 years before the dementia diagnosis [52]. Addressing the uncertain causal role of overweight and obesity in cognitive performance and the risk of dementia is thus important.

Cohort studies have observed an association between midlife obesity and the risk of dementia. In the ARIC study, 5,995 participants (with a mean age of 57 years) were followed up for 20 to 25 years [56]. Obesity in late midlife was observed to be associated with an increased risk of late life MCI and dementia. In the Whitehall II Study, 10,308 participants aged 35 to 55 years at baseline were followed up for 28 years, and their BMI was assessed six times during the follow-up [74]. Leveraging this data, obesity (BMI ≥30 kg/m^2) at the age of 50 years but not at 60 or 70 years

was found to be associated with increased risk of dementia compared to those with BMI <30kg/m^2. The BMI of the participants diagnosed with dementia during the follow-up was found to decline years before dementia diagnosis. Furthermore, in a meta-analysis of prospective studies with a total of 25,624 participants, underweight, overweight, and obesity in midlife were associated with an increased risk of later life dementia [75], indicating that the association of BMI with the risk of dementia may be nonlinear. However, conflicting results were found in a large-scale cohort study from the United Kingdom Clinical Practice Research Datalink, in which almost two million participants aged ≥40 years (with the median age of 55 years) were followed up for an average of 9.1 years [76]. This study found underweight in middle age and old age to be associated with an increased risk of dementia; however, the association between midlife obesity and the risk of dementia was not observed when the normal weight group was used as a reference.

The findings of the cohort studies that examined the associations between obesity and cognitive performance are similar. In the Swedish Adoption/Twin Study of Aging, 657 participants with a mean age of 40 years at baseline were followed up for 21 years [77]. Their BMI was measured twice during the follow-up period, and their cognitive performance was assessed every three years. Overweight/obesity in early midlife was found to be associated with poorer cognitive performance in late life compared to normal weight and, additionally, with a steeper decline in perceptual speed. Moreover, underweight and overweight/obesity in late midlife were found to be associated with lower cognitive abilities in late life. In another report from the Baltimore Longitudinal Study of Aging, 1,703 participants aged 19 to 93 years (with a mean age of 56 years at baseline) were followed up repeatedly every two to three years for an average of 3.1 examinations [78]. This study found that a higher BMI and waist-to-hip ratio were inversely associated with global cognition, memory, and verbal fluency. Also, contradictory results were reported because a higher BMI was found to be associated with better attention and visuospatial ability. Furthermore, in the Study of Women's Health Across the Nation, 1,139 participants (with a mean age of 53 years at baseline) were followed up for 10 years [79]. Increased waist circumference in midlife was found to be associated with an accelerated cognitive decline in processing speed. In addition, in the Framingham Heart Study, 1,423 participants (with a mean age of 66 years at baseline) were followed up for 18 years, and their cardiovascular risk factors were measured repeatedly every two years [60]. Obesity was found to be inversely associated with learning and memory among men.

Moreover, an association between adulthood obesity and midlife cognitive performance has been observed. In the Jerusalem Lipid Research Clinic Study, 507 participants aged 17 at baseline were followed up for 33 years, and after that, their cognitive performance was assessed when they were between 48 to 52 years [80]. In this study, higher BMI in adolescence and cumulative exposure to higher BMI

between adolescence and midlife were found to be inversely associated with global cognitive performance. However, the association was present only among participants with low SES. Additionally, in the 1946 British Birth Cohort, 1,249 participants were followed up for 30 years [81]. Their BMI and waist circumference were measured repeatedly during the follow-up, and their cognitive performance was assessed at the end of the follow-up, when they were between 60 and 64 years. It was observed that a longer exposure time to elevated waist circumference or BMI was inversely associated with memory and reaction time. Furthermore, faster gain of waist circumference or BMI was found to be associated with the largest decline in memory and a longer reaction time.

Short-term studies on the association between being overweight and cognitive performance in childhood have indicated contradictory results. In two cross-sectional studies, overweight in childhood was found to be associated with worse cognitive performance [82,83]. In a study from the Third National Health and Nutrition Examination Survey with 2,519 eight- to 16-year-old children and adolescents, a high BMI was found to be associated with worse visuospatial organization and general mental ability [82]. Moreover, in a study from the OPUS School Meal Study, normal weight compared to overweight and underweight was observed to be associated with better cognitive performance and school performance in 828 children between eight and 11 years [83]. However, a longitudinal study from the Quebec Longitudinal Study of Child Development with 1,959 children who were followed up from the age of four to the age of seven years found no association between overweight and cognitive performance or school performance [84]. Instead, compared to normal weight, underweight was found to be associated with worse cognitive performance and school performance.

In conclusion, the prior evidence on the association between midlife overweight and worse cognitive performance is solid, while the observations of the association between childhood overweight and worse cognitive performance in childhood are not quite consistent. However, it might be speculated that childhood obesity starts to influence on cognitive performance in adulthood or in midlife.

2.4.3.4 Type 2 diabetes and impaired fasting glucose

According to the WHO, type 2 diabetes is diagnosed if the fasting plasma glucose is ≥ 7.0 mmol/l, if the plasma glucose is ≥11.1 mmol/l two hours after ingestion of 75 g oral glucose load, or if the glycated hemoglobin (HbA1c) ≥48 mmol/mol (≥6.5 %) [85]. Impaired fasting glucose is diagnosed if the fasting plasma glucose is 6.1 to 6.9 mmol/l and, at the same time, (if measured) the plasma glucose is <7.8 mmol/l two hours after ingestion of 75 g oral glucose load [85]. In AHA's Life's Simple 7 ideal cardiovascular health metrics, fasting blood glucose <5.6 mmol/l (HbA1c <39

mmol/mol) is considered to indicate ideal, fasting blood glucose 5.6 to 6.9 mmol/l (HbA1c 39 to 47 mmol/mol) or treated to goal intermediate, and fasting blood glucose ≥7.0 mmol/l (HbA1c ≥48 mmol/mol) poor cardiovascular health [54]. Diabetes is a major risk factor for cardiovascular diseases, including coronary heart disease and stroke [54]. Furthermore, prior evidence indicates that diabetic and prediabetic risk factor levels are not only linked to an increased risk of dementia but also poorer cognitive performance.

Type 2 diabetes in late life is acknowledged by the Lancet Commission as a significant risk factor for the risk of dementia [3]. However, evidence from previous studies indicates that glucose metabolism might exert its influence earlier. For example, in observational studies, diabetes since midlife was observed to be associated with the risk of dementia. In the ARIC study, 5,995 participants (with a mean age of 57 years at baseline) were followed up for 20 to 25 years [56]. Diabetes in midlife was found to be associated with increased risk of late life MCI and dementia. Moreover, in a cohort study on the members of the Kaiser Permanente Medical Care Program of Northern California, cardiovascular risk factors were measured among 8,845 participants in midlife between the ages of 40 and 44, who were then followed up for an average of 26.7 years [57]. It was observed that diabetes in midlife was associated with an increased risk of dementia.

Diabetes has also been shown to be associated with poorer cognitive performance. In the Tromsø study, 5,033 participants' (with a mean age of 58 years at baseline) cardiovascular risk factors were measured at baseline, and their cognitive performance was assessed after seven years of follow-up [58]. According to the findings of this study, diabetes was independently associated with worse verbal memory and processing speed in men and processing speed in women. Furthermore, in a cross-sectional study from the Framingham Heart Study, 2,126 participants' cognitive performance was assessed at a mean age of 40 years, and brain MRI was performed on 1,597 participants [86]. In that report, type 2 diabetes was found to be associated with worse memory, visual perception, and attention performance. Type 2 diabetes was also related to increased white matter hyperintensity and decreased total cerebral brain and occipital lobar gray matter volumes. In addition, in the Study of Women's Health Across the Nation, 1,139 participants (with a mean age of 53 years at baseline) were followed up for 10 years, and diabetes and elevated fasting glucose in midlife were found to be associated with an accelerated decline in processing speed [79]. Additionally, a systematic review and meta-analysis of cross-sectional and prospective studies between adulthood and old age found that type 2 diabetes and impaired glucose metabolism were associated with worse cognitive performance [63].

In younger cohorts, impaired glucose levels have been observed to be associated with poorer cognitive performance. In the CARDIA, 3,381 participants aged 25

years (ranging between 18 and 30 years) at baseline were followed up for 25 years. Greater cumulative exposure to higher fasting blood glucose levels, especially the levels above the recommended guidelines, was found to be associated with worse executive function, processing speed, and verbal memory [61]. Also, in the Australian Diabetes, Obesity and Lifestyle Study, 4,547 participants (two groups aged 25 to 59 years and >60 years) were followed up for 12 years, and their fasting plasma glucose and HbA1c were assessed thrice during the follow-up [87]. In both age groups, those with type 2 diabetes, those who were younger males with high nondiabetic HbA1c, and those with high-stable blood glucose were found to have poorer cognitive performance at the end of the follow-up. Moreover, in the Jerusalem Lipid Research Clinic Study, 505 nondiabetic participants were followed up for an average of 13.1 years, and their fasting glucose and glucose levels two hours after ingestion of 75 g oral glucose load were assessed at the mean age of 30 and after the follow-up [88]. Fasting glucose ≥5.6 mmol/l at the age of 30 was found to be associated with worse visual-spatial processing and attention. However, insulin resistance, changes in fasting glucose, and glucose levels two hours after the ingestion of 75 g oral glucose load were not found to be associated with cognitive performance. Therefore, the previous studies on adults suggest that fasting glucose levels might influence cognitive performance earlier than believed.

The detailed mechanisms for diabetes and impaired glucose levels are uncertain. Insulin resistance has been suggested to lead to adverse microvascular and neuronal metabolic alterations within the brain [87]. However, insulin resistance was not associated with structural brain changes in the Framingham Heart Study [86], although the authors argued that insulin resistance, as it may have a role in other cellular pathways, does not necessarily reflect peripheral changes. Instead, they hypothesized that since increased fasting glucose has a role in white matter hyperintensity, it may contribute to ischemic cerebrovascular disease, which, in turn, may cause neuronal apoptosis and brain atrophy through impaired blood flow to the neurovascular unit. Hyperglycemia may also increase the formation of advanced glycation end products, which increase oxidative stress, cross-linking of amyloid fibrils, modification of cytoskeletal tau proteins, and inflammation in the brain [86]. For example, increased oxidative stress was observed in a study conducted on diabetic mice [89].

2.4.4 Risk factor accumulation

Cardiovascular risk factors tend to accumulate [90–94]. Previous studies have typically examined the role of a single cardiovascular risk factor in cognitive performance or the risk of dementia. Although these studies often used other cardiovascular risk factors to adjust the associations, they did not take into account

the combinations and context in which the risk occurs [3]. Cardiovascular risk factor accumulation may thus have a significant life-course role in later life cognitive health.

Different risk scores are used to predict adverse cardiovascular outcomes (cardiovascular diseases, coronary heart disease, and stroke) and dementia [90–94]. The commonly used risk scores are the Finnish Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study Risk score [90], the Framingham Risk Scores [91–93], and AHA's Life's Simple 7 ideal cardiovascular health metrics [94]. In the risk scores, older individuals were observed to have more adverse cardiovascular risk factors and higher cardiovascular risks. The risk scores are also used to examine the association between cardiovascular risk factor accumulation and cognitive performance or the risk of dementia. In addition, several other methods are also used to assess cardiovascular risk factor accumulation, such as calculating various scores that indicate the number of adverse risk factors—for example, the number of unhealthy behaviors (smoking, alcohol abstinence, low physical activity, and low fruit and vegetable consumption) [95].

The CAIDE Study Risk Score, developed to predict the risk of dementia based on midlife cardiovascular risk factor accumulation [90], includes age, sex, education, systolic blood pressure, BMI, total cholesterol, physical activity, and APOE genotype with specific weight. The Framingham Risk Scores are generally used to predict the 10-year probability of adverse cardiovascular outcomes. Different risk scores have been developed for cardiovascular disease, coronary heart disease, and stroke. The Framingham Coronary Heart Disease Risk Profile [91], the Framingham Cardiovascular Disease Risk Profile [92], and the Framingham Stroke Risk Profile [93] include age, sex, systolic blood pressure, HDL cholesterol, total cholesterol, smoking, and diabetes with specific weight. In the Framingham Stroke Risk Profile, cardiovascular diseases, atrial fibrillation, and left ventricular hypertrophy are included as well.

Furthermore, the AHA has defined ideal cardiovascular health on seven health behaviors and health factors (Life's Simple 7). Ideal cardiovascular health metrics include nonsmoking, BMI <25 kg/m^2, physical activity at goal levels, pursuit of a diet consistent with the current guideline recommendations, untreated total cholesterol <5.172 mmol/l, untreated blood pressure <120/<80 mmHg, and fasting blood glucose <5.6 mmol/l [94]. The AHA's Life's Simple 7 ideal cardiovascular health metrics are often used to study the association between cardiovascular risk factor accumulation and cognitive performance.

In previous studies (Table 1), the cardiovascular risk factor accumulation in midlife was found to be associated with the risk of dementia in later life. The cardiovascular risk factors in a cohort of the members of the Kaiser Permanente Medical Care Program of Northern California were measured in midlife [57]. After

an average follow-up duration of 26.7 years, the accumulation of risk factors (smoking, hypertension, high total cholesterol, diabetes) in midlife was found to be associated with an increase in the risk of dementia in a dose-responsive manner. In another cohort of CAIDE study participants, the participants with both high systolic blood pressure (≥160 mmHg) and high total cholesterol (≥6.5 mmol/l) in midlife were found to have a higher risk of Alzheimer's disease than those participants with only one of the risk factors after an average of 21 years of follow-up [55]. A similar association was observed in the Chicago Heart Association Detection Project in Industry Study with younger participants (with an age range between 23 and 47 years at baseline), where favorable cardiovascular health (blood pressure, total cholesterol, nonsmoking, BMI, diabetes) in midlife was found to be associated with decreased risk of dementia after a long follow-up (43 years) [96].

In observational studies with old-aged participants, cardiovascular risk factor accumulation was found to be associated with worse cognitive performance. In the Framingham Heart Study, the cardiovascular risk factors were measured repeatedly every two years during an 18-year follow-up on participants with a mean age of 66 years at baseline [60]. In this study, among men, the accumulation of both hypertension and obesity was associated with worse cognitive performance. The presence of both risk factors resulted in worse cognitive performance compared to the presence of either one or none of the risk factors. Furthermore, in a cross-sectional study from the Maine-Syracuse Longitudinal Study, the AHA's Life's Simple 7 ideal cardiovascular health metrics were assessed at the mean age of 61 years [97]. A higher AHA's Life's Simple 7 ideal cardiovascular health metrics score was associated with better global cognitive performance, visual-spatial memory, and working memory. Additionally, in the 3C Study, old-aged participants (with a mean age of 74 years) were followed up for an average of 8.5 years [98]. An increased number of the AHA's Life's Simple 7 ideal cardiovascular health metrics was associated with a lower risk of dementia and a lower rate of decline in memory and global cognition.

There are a great number of observational studies on cardiovascular risk factor accumulation in midlife and its association with midlife or later life cognitive performance. Many of these studies assessed the relationship between risk factor accumulation and changes in cognitive performance, which is more accurate for examining the causality of risk factors. In the CARDIA study, cognitive performance was assessed in midlife (with a mean age of 50 years) and five years later [99]. A higher number of adverse cardiovascular risk factors (obesity, smoking, hypertension, diabetes, and high total cholesterol) and a higher Framingham Coronary Heart Disease Risk Score were associated with accelerated cognitive decline. Moreover, in a report from the Personality and Total Health Through Life Project, the participants (aged 40 to 44 years at baseline) were followed up for eight

years, and their cognitive performance was assessed thrice during the follow-up [100]. The study found that a greater accumulation of adverse cardiovascular risk factors (smoking, hypertension, depression, high BMI, diabetes, low physical activity) was associated with faster decline in processing speed and reaction time. Additionally, adverse individual risk factors were found to be associated with poorer memory and verbal ability. In another report from the Whitehall II cohort, middle-aged participants were followed up for 10 years, and their cognitive performance was assessed thrice during the follow-up [101]. An adverse Framingham Stroke Risk Profile was associated with a faster decline in verbal fluency, vocabulary, and global cognition. Of the individual components from the Framingham Stroke Risk Profile, diabetes was associated independently with a faster decline in global cognition. Furthermore, in the English Longitudinal Study of Ageing, participants aged 50 to 79 years were followed up for 10 years, and their cardiovascular risk factors—including diabetes, hypertension, smoking, physical inactivity, and obesity—were assessed at baseline [102]. Leveraging this data, an increased number of adverse cardiovascular risk factors was found to be associated with memory decline in the younger half of the group but not in the older half. Additionally, in the Prevention of Renal and Vascular End-stage Disease cohort, participants aged ≥35 years (with a mean age of 54 years) were followed up for 5.5 years, and their cognitive performance was assessed thrice during the follow-up [103]. It was observed that an increased score in the Framingham Risk Score for Cardiovascular Disease was associated with cognitive decline, which was measured as a composite score from two cognitive tests that measured executive function and memory and learning. Moreover, middle-aged participants were followed up for 20 years in the ARIC study. The AHA's Life's Simple 7 ideal cardiovascular health metrics were assessed in midlife, and their cognitive performance was assessed repeatedly during the follow-up [104]. A higher score in AHA's Life's Simple 7 ideal cardiovascular health metrics and individual metrics, particularly ideal blood pressure and ideal fasting glucose, was associated with better cognitive performance in midlife and reduced cognitive decline.

In many studies that examined midlife risk factor association with cognitive performance, cognitive performance was assessed once. Of these studies, only one assessed the cardiovascular risk factor accumulation longitudinally. In the Whitehall II cohort study, participants with a mean age of 44 years were followed up for 17 years, and their unhealthy behaviors (smoking, alcohol consumption, low physical activity, and low fruit and vegetable consumption) were assessed using questionnaires thrice during the follow-up [95]. The number and the exposure time of unhealthy behaviors were found to be inversely associated with executive function and memory at the mean age of 61 years.

Other observational studies assessed risk factor accumulation only once. In the Framingham Offspring Study, participants with a mean age of 54 years at baseline were followed up for an average of 14.1 years [105]. A worse Framingham Stroke Risk Profile was associated with poorer executive function. Of the individual risk factors, diabetes was inversely associated with executive function. In another study, participants aged ≥45 years at baseline in the Supplémentation en Vitamines et Minéraux Antioxydant Study were followed up for an average of 13.4 years, and their cognitive performance was assessed after, at the mean age of 65.5 years [106]. The association between cognitive performance and different risk profiles was studied: Framingham Coronary Heart Disease Risk Profile, Framingham Cardiovascular Disease Risk Profile, and Framingham Stroke Risk Profile. All the Framingham Risk Profiles assessed at midlife were inversely and uniformly associated with poorer global cognitive performance and, especially, verbal memory. Furthermore, in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the participants (with a mean age of 52 years at baseline) were followed up in previous national examinations for an average of 17.6 years before the FINGER baseline examinations, when cognitive testing was performed, and a subgroup of 132 participants underwent MRI [107]. A higher CAIDE Study Risk Score at baseline was related to more pronounced deep white matter lesions, lower total gray matter and hippocampal volume, lower cortical thickness, poorer executive function, processing speed, memory, and MMSE. Moreover, in the older Finnish Twin Cohort, middle-aged participants were followed up for an average of 22.6 years, and afterwards their cognitive performance was assessed using a validated telephone interview [108]. The CAIDE Study Risk Score at baseline was inversely associated with cognitive performance. Also, individual risk factors—including midlife obesity, hypertension, and low physical activity—increased the risk of poorer cognitive performance. In addition, in the Study of Women's Health Across the Nation, middle-aged women were followed up for 10 years, and a higher heart age computed from the Framingham Cardiovascular Disease Risk Profile in midlife was found to be associated with accelerated cognitive decline in processing speed [79]. Additionally, in the Hoorn Study, after a 15-year follow-up, a higher CAIDE Study Risk Score in midlife was found to be associated with worse information processing speed, visuoconstruction, and abstract reasoning [109].

In addition, cross-sectional studies with middle-aged participants assessed the association between cardiovascular risk factor accumulation and cognitive performance. In a cross-sectional study from the Hispanic Community Health Study and Study of Latinos with participants aged 45 to 74 years, an increased score of the AHA's Life's Simple 7 ideal cardiovascular health metrics was found to be associated with better verbal learning, memory, verbal fluency, and psychomotor

speed [110]. In another cross-sectional study from the Emory Twins Study, an increased score of the AHA's Life's Simple 7 ideal cardiovascular health metrics in midlife was found to be associated with better processing speed and memory [111]. Additionally, in a cross-sectional study from the Gipuzkoa Alzheimer Project, a higher CAIDE Study Risk Score in midlife was found to be associated with worse executive function and visual perception and construction [112].

Few of the previous studies had follow-up time starting before midlife, meaning that the association between cardiovascular risk factor accumulation since childhood or adulthood and cognitive performance is obscure. The CARDIA is the only prior study with prospective data from young adulthood to midlife (baseline age 18 to 30 years), and with results suggesting an adverse association between longitudinally assessed cardiovascular risk factor accumulation and cognitive performance [113]. In the CARDIA, the participants were followed up for 25 years, and the AHA's Life's Simple 7 ideal cardiovascular health metrics were assessed thrice at baseline and in follow-up examinations at years seven and 25. The results suggest that having a greater score of the AHA's Life's Simple 7 ideal cardiovascular health metrics in young adulthood and middle age is independently associated with better visual motor speed, executive function, and verbal memory in midlife. Furthermore, BMI, blood pressure, glucose, and total cholesterol were assessed at the age of 27 years in the Study of Healthy Aging in African Americans [114]. After an average of 42 years of follow-up, an increased number of adverse cardiovascular risk factors in adulthood were associated with worse executive function and verbal memory. Moreover, in a previous report from the Young Finns Study (this thesis' study population), the participants were followed up for 31 years since childhood and adolescence (aged between three and 18 years at baseline) [64]. Cardiovascular risk factor accumulation (systolic blood pressure, LDL cholesterol, smoking) in childhood and adolescence in levels that exceeded the risk factor guidelines was found to be associated with poorer memory and associative learning in early midlife, independent of the risk factor levels in early midlife. Additionally, in a Chinese cross-sectional study on 3,798 children aged between six and 12 years, having a greater score of the AHA's Life's Simple 7 ideal cardiovascular health metrics was found to be associated with better executive function [115].

In conclusion, the findings of several cohort studies (Table 1) indicate that midlife cardiovascular risk factor accumulation is associated with worse cognitive performance and an increased risk of dementia. However, the Young Finns Study and the CARDIA study have highlighted the potential role of early life cardiovascular risk factor levels and risk factor accumulation for this association earlier than believed. For example, in the Lancet Commission's statement, largely because no observational studies have been conducted since childhood, many risk factors are acknowledged only from midlife and later in life [3].

Table 1. Major observational studies examining association between cardiovascular risk factor accumulation and cognitive performance or risk of dementia.

Cohort [ref.]	N	Country	Follow-up time, years	Age at baseline	Indicator of cardiovascular risk factor accumulation	Outcome
Young Finns Study [64]	2,026	Finland	31	3-18	Systolic blood pressure, LDL cholesterol, smoking	Cognitive performance
CARDIA Study [113]	2,932	USA	25	18-30	AHA's Life's Simple 7	Cognitive performance
Study of Healthy Aging in African Americans [114]	764	USA	42	27	Obesity, blood pressure, glucose, total cholesterol	Cognitive performance
Personality and Total Health Through Life Project [100]	2,530	Australia	8	40-44	Smoking, hypertension, depression, obesity, diabetes, physical inactivity	Cognitive decline
Whitehall II Study [95]	5,123	UK	17	44	Smoking, alcohol consumption, physical inactivity, low fruit and vegetable consumption	Cognitive performance
CARDIA Study [99]	2,675	USA	5	50	Obesity, smoking, hypertension, diabetes, total cholesterol, and Framingham Coronary Heart Disease Risk Score	Cognitive decline
FINGER Study [107]	1,260	Finland	17.6	52	CAIDE Study Risk Score	Cognitive performance
Finnish Twin Cohort [108]	2,165	Finland	22.6	52	CAIDE Study Risk Score	Cognitive performance
Supplémentation en Vitamines et Minéraux Antioxydant Study [106]	3,061	France	13.4	≥45	All Framingham Risk Profiles	Cognitive performance
Study of Women's Health Across the Nation [79]	1,139	USA	10	53	Framingham Cardiovascular Disease Risk Profile	Cognitive decline
ARIC Study [104]	13,270	USA	20	54	AHA's Life's Simple 7	Cognitive decline
Prevention of Renal and Vascular End-stage Disease Study [103]	3,572	Netherlands	5.5	54	Framingham Risk Score for Cardiovascular Disease	Cognitive decline

Cohort [ref.]	N	Country	Follow-up time, years	Age at baseline	Indicator of cardiovascular risk factor accumulation	Outcome
Framingham Offspring Study [105]	1,755	USA	14.1	54	Framingham Stroke Risk Profile	Cognitive performance
Whitehall II Study [101]	5,810	UK	10	56	Framingham Stroke Risk Profile	Cognitive decline
Hoorn Study [109]	322	Netherlands	15	56	CAIDE Study Risk Score	Cognitive performance
English Longitudinal Study of Ageing [102]	4,372	UK	10	50-79	Diabetes, hypertension, smoking, physical inactivity, obesity	Cognitive decline
Framingham Heart Study [60]	1,423	USA	18	66	Hypertension and obesity	Cognitive performance
3C Study [98]	6,626	France	8.5	74	AHA's Life's Simple 7	Risk of dementia and cognitive decline
City of Guangzhou [115]	3,798	China	Cross-sectional	6-12	AHA's Life's Simple 7	Cognitive performance
Hispanic Community Health Study and Study of Latinos [110]	9,623	USA	Cross-sectional	45-74	AHA's Life's Simple 7	Cognitive performance
Emory Twins Study [111]	544	USA	Cross-sectional	55	AHA's Life's Simple 7	Cognitive performance
Gipuzkoa Alzheimer Project [112]	375	Spain	Cross-sectional	58	CAIDE Study Risk Score	Cognitive performance
Maine-Syracuse Longitudinal Study [97]	972	USA	Cross-sectional	61	AHA's Life's Simple 7	Cognitive performance
Chicago Heart Association Detection Project in Industry Study [96]	10,119	USA	43	23-47	Blood pressure, total cholesterol, nonsmoking, BMI, diabetes	Risk of dementia
Kaiser Permanente Medical Care Program of Northern California [57]	8,845	USA	26.7	40-44	Smoking, hypertension, total cholesterol, diabetes	Risk of dementia
CAIDE Study [55]	1,449	Finland	21	50	Systolic blood pressure and total cholesterol	Risk of dementia

2.4.5 Lifestyle risk factors

2.4.5.1 Physical activity

Since physical activity plays a major role in maintaining cardiovascular and cognitive health, physical inactivity has been acknowledged as a persistent public health problem that results in a high burden of cardiovascular diseases and other noncommunicable chronic diseases [116]. On a global scale, it has been estimated that 81% of adolescents (75% of adolescents in Finland) aged 11 to 17 years are not meeting the current recommendations for daily physical activity [6]. The latest physical activity guidelines were published by the WHO in 2020.

According to the 2020 WHO guidelines on physical activity and sedentary behavior, all adults should undertake 150 to 300 min of moderate-intensity or 75 to 150 min of vigorous-intensity physical activity, or some equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity per week [117]. The WHO guidelines recommend that children and adolescents engage in an average of 60 min/day of moderate-to-vigorous intensity aerobic physical activity every week. For all age groups, regular muscle-strengthening activities are recommended. Reducing sedentary behaviors is also recommended for all age groups and abilities. Furthermore, according to the latest Finnish physical activity recommendations, published by the UKK Institute in 2019 [118], all adults should undertake 150 min of moderate-intensity or 75 min of vigorous-intensity physical activity per week. For children and adolescents, an average of 60 min/day of moderate-to-vigorous intensity aerobic physical activity is recommended. Moreover, for all age groups, muscle-strengthening or mobility activities are recommended at least twice a week.

Meeting the physical activity guidelines reduces mortality and cardiovascular disease risk to about 75%, which is close to the maximal benefit possible to obtain through physical activity alone [119]. However, any moderate-to-vigorous physical activity is better than none, and beneficial health outcomes begin when adopting even a modest (one-third of guidelines) amount of physical activity. Thus, healthcare systems, clinical and community care providers, fitness professionals, the technology industry, and other stakeholders need concrete means to catalyze the increased adoption of physical activity assessment and promotion and to ensure that the physical activity guidelines are met [116].

In addition to cardiovascular diseases, higher physical activity may be associated with better life-course SES and cognitive health. In the Lancet Commission statement, physical inactivity has been acknowledged only as a later life risk factor for dementia [3]. It is important to note that engaging in physical activities from childhood has already been shown to link with several beneficial factors in childhood, such as academic achievement and cognitive ability [120]. Also, the

associations between physical activity and cognitive performance are multifaceted. In the Young Finns Study (the study population of this thesis), physical activity in childhood was observed to be associated with academic [121] and labor market [122] success later in life. However, education was observed to be associated with a physically active lifestyle [123], which raises the question about the causal relations between physical activity and different outcomes, such as cognitive performance. It is important to note that the causal role of physical activity in cognitive performance is supported by evidence from previous randomized controlled trials indicating a direct association between moderate-to-vigorous intensity physical activity in childhood and childhood cognitive performance as well as moderate-to-vigorous intensity physical activity in old age and cognitive performance and risk of dementia in old age [124]. However, there are limited data for randomized controlled trials regarding the associations of physical activity in childhood, adolescence, and midlife with cognitive performance, as it is nearly impossible to perform randomized control trials to test the life-course causal relations between physical activity and cognitive performance in humans. Nonetheless, there is solid observational evidence on the association between midlife and old age physical activity, cognitive performance, and risk of dementia [3].

The majority of observational studies have indicated the association of higher physical activity with a lower risk of dementia. In a study from the Finnish Twin Cohort, 21,791 participants aged between 24 and 60 years were followed up for 29 years, and their physical activity was assessed twice during the follow-up [125]. Higher physical activity was observed to be associated with lower dementia mortality. Moreover, in the CAIDE study, physical activity was assessed in midlife at the mean age of 50 years in 1,449 participants, who were followed up for an average of 21 years [126]. Higher physical activity in midlife was observed to be associated with a reduced risk of dementia and Alzheimer's disease. Furthermore, in the Cardiovascular Health Cognition Study, physical activity was assessed once in 3,375 participants aged ≥65 years (with a mean age of 75 years) and followed up for an average of 5.4 years [127]. Leveraging these data, an association between lower physical activity and increased risk of dementia was observed. Additionally, in a large-scale Swedish study among 1.1 million male conscripts, both lower cardiovascular fitness in the cycle ergometer test and worse cognitive performance at the age of 18 were associated with an increased risk of early-onset dementia and MCI later in life (a median follow-up time of 27 years) [128]. While lower cardiovascular fitness might indicate lower physical activity, it is important to note that it might also indicate other factors, as some physical activities do not necessarily help in developing cardiovascular fitness.

However, one large cohort study observed no association between physical activity and the risk of dementia. In the Whitehall II Study, 10,308 participants aged

between 35 and 55 years were followed up for 27 years, and no association was observed between physical activity and repeatedly measured cognitive performance or risk of dementia [129]. Moreover, a decline in physical activity levels was observed to begin in people with dementia nine years before they were diagnosed. This underlines a possibility for bias caused by reverse causation, where a decline in physical activity may be a manifestation of preclinical dementia. However, according to a prior report from the Whitehall II cohort, low physical activity was associated with poorer fluid intelligence in participants aged between 46 and 68 years, both cross-sectionally at baseline as well as longitudinally during an 11-year follow-up [130].

In old-aged populations, high physical activity has been shown to be associated with better cognitive performance. For example, in the Age Gene/Environment Susceptibility–Reykjavik Study, physical activity was queried in midlife at the mean age of 51 years, and cognitive performance was assessed after 26 years of follow-up in 4,945 participants [131]. In this study, higher physical activity in midlife was observed to be associated with better processing speed, memory, and executive function and a lower risk of dementia. Furthermore, in the English Longitudinal Study of Aging, 10,652 participants aged ≥50 years (with a mean age of 65 years at baseline) were followed up for 10 years [132]. Their physical activity was queried at baseline, and their cognitive performance was assessed at two-year intervals. Low physical activity was found to be associated with an accelerated decline in memory and executive function in women and an accelerated decline in executive function in men. Additionally, randomized controlled trials have supported the causal relationship between higher old age physical activity and better cognitive performance in old age [124].

In adult to middle-aged populations, higher physical activity has been shown to be associated with better cognitive performance. In the British 1946 birth cohort study of 1,919 participants, physical activity was assessed at the age of 36 and cognitive performance was assessed at 43 and 53 [133]. High physical activity was observed to be associated with better memory function at 43 and a slower rate of cognitive decline in memory function from 43 to 53. However, contradictory observations have also been reported. In the Study of Women's Health Across the Nation, 1,718 women (with a mean age of 46 years at baseline) were followed up for an average of 11.9 years, and their cognitive performance was assessed thrice during the follow-up [134]. In this study, no association was observed between repeatedly measured physical activity and cognitive decline after controlling for confounders. Nevertheless, a systematic review and meta-analysis of longitudinal observational studies on participants aged ≥40 years concluded that higher levels of physical activity are associated with a reduced risk of cognitive decline and dementia [135].

In younger populations, higher physical activity has been shown to be associated with better cognitive performance in early life. In a prospective Brazilian birth cohort study of 3,235 participants, physical activity throughout adolescence was found to be directly associated with intellectual quotient at the age of 18 [136]. Furthermore, in a cross-sectional Spanish study of 1,820 participants (aged between 13 and 18 years), physical activity was found to be directly associated with verbal ability, numeric ability, and reasoning ability [137]. Randomized controlled trials have also supported the causal relationship between childhood and adolescence physical activity and cognitive performance in early life [124].

The association between early life physical activity and cognitive performance in midlife or later in life has not been studied much, as life-course observational studies with comprehensive data do not exist. In many studies, life-course physical activity was assessed using retrospective questionnaires. In a retrospective study of 9,344 women aged ≥65 years (with a mean age of 72 years), physical activity was retrospectively queried from teenage, 30 years of age, 50 years of age, and late life [138]. High life-course and, especially, teenage physical activity was found to be associated with less decline in modified MMSE. Moreover, in the Longitudinal Aging Study Amsterdam, cognitive performance was assessed in 1,241 participants between ages 62 to 85 and physical activity between ages 15 to 25 was queried retrospectively [139]. A direct association between physical activity and information processing speed was observed among men. Furthermore, in the Brain in Motion study, 226 participants (with a mean age of 67 years) provided retrospective life-course physical activity information, which indicated a direct association of life-course physical activity with cognitive performance measured using a comprehensive neuropsychological assessment [140]. Additionally, in the Lothanian Birth Cohort 1921 study, cognitive performance was assessed up to four times at 79, 83, 87, and 90 years of age, and details about earlier life physical activity were queried retrospectively [141]. Higher later life (60 to 75 years) physical activity was observed to be associated with less cognitive decline, while the association of early life and midlife physical activity was not observed. These studies that retrospectively assessed physical activity indicate a plausible association between higher early life physical activity and better cognitive performance later in life. However, retrospective assessment may be prone to bias due to inaccurate recall or measurement of physical activity. In addition, the previous studies did not assess physical activity since childhood.

Only a few prospective cohort studies have reported associations between early life physical activity and cognitive performance. In the CARDIA study, 3,247 participants aged between 18 and 30 years were followed up for 25 years, and their physical activity was repeatedly assessed at least three times during the follow-up [7]. Low physical activity was found to be associated with worse executive function

and processing speed. Moreover, in the UK National Child Development Study, cognitive performance was assessed in 9,649 participants at the age of 50, and their physical activity was queried repeatedly between the ages of 11 and 50 years [142]. Life-course physical activity was observed to be associated directly with memory and executive function. Furthermore, in a report from the Personality and Total Health Through Life Project, physical activity and cognitive performance were assessed thrice during an eight-year follow-up on participants aged 20 to 24, 40 to 44, and 60 to 64 years at baseline [143]. In all age groups, pronouncedly in the youngest, physical activity predicted better baseline fluid cognitive ability, though an association between physical activity and cognitive decline was not observed.

As evident from the prior literature, there remains a knowledge gap concerning the longitudinal association between early life physical activity and adulthood cognitive performance, as it was not possible for any prior study to apply longitudinally collected data on physical activity beginning from childhood. Furthermore, previous studies did not consider physical activity levels from other age windows, such as adulthood, as possible confounders. This restrains the possibility of interpreting the independent carry-over associations of early life physical activity with midlife cognitive performance.

2.4.5.2 Smoking

Tobacco smoking increases the risk of death [144], generating thousands of different compounds, including nicotine, access to the body. Many of these compounds are toxic to the cardiovascular and pulmonary systems. Moreover, smoking causes several adverse changes to brain functions. There is sufficient epidemiologic evidence that links a smoking history to preclinical changes in the brain (atrophy, silent infarcts, increase in white matter hyperintensity volume), accelerated cognitive decline (executive function, verbal memory, processing speed), and increased risk of dementia (Alzheimer's disease and vascular dementia) [145].

For example, in a cohort study on the members of the Kaiser Permanente Medical Care Program of Northern California, cardiovascular risk factors were measured in 8,845 participants in midlife between the ages of 40 and 44 and followed up for an average of 26.7 years [57]. Smoking at midlife was observed to be associated with an increased risk of dementia. Another example is the Tromsø study, where 5,033 participants' (with a mean age of 58 years at baseline) cardiovascular risk factors were measured at baseline, and their cognitive performance was assessed after a seven-year follow-up [58]. Smoking was found to be independently associated with poorer verbal memory and processing speed. Furthermore, in the Monitoring Project on Cardiovascular Disease Risk Factors study, 1,927 participants (with a mean age of 56 years at baseline) were followed up for approximately five years and,

afterwards, their cognitive performance was assessed [146]. Current smokers were observed to have reduced psychomotor speed and reduced cognitive flexibility compared with never smokers. Moreover, in the Whitehall II Study, 5,388 participants' cognitive performance was assessed (with a mean age of 56 years), and of these, 4,659 were retested five years later [144]. According to the findings from this study, compared with nonsmokers, smokers were more likely to have poorer memory function. However, during the five-year follow-up, smoking was not observed to be associated with cognitive decline.

Additionally, two studies from the Young Finns Study population (the study population of this thesis) found that smoking in early life was associated with poorer episodic memory and associative learning in midlife [64]. In another report from the Young Finns Study cohort, exposure to parental smoking in childhood was found to be associated with worse memory and learning function in adulthood and midlife [147]. These observations from the Young Finns Study and other previous studies suggest that smoking influences cognitive performance earlier than believed. For example, in the Lancet Commission's statement, smoking is acknowledged as a later life risk factor for dementia [3].

2.4.5.3 Dietary habits

Diet is an important lifestyle factor; it can possibly modify cognitive performance and the risk of dementia [148]. Certain nutrients—folate, flavonoids, vitamin D, and certain lipids—have a protective association with cognitive outcomes in older people [148]. Furthermore, different food groups—seafood, vegetables, and fruits—are possibly related to better cognitive outcomes [148].

A large-scale umbrella review presented sufficient evidence for the association between adherence to a Mediterranean diet, less cognitive decline, and a lower risk of dementia [149]. Following a Mediterranean diet usually involves high consumption of fruits, vegetables, wholegrains, olive oil, fermented dairy products, nuts, seed, herbs, and seafood [148]. According to the results of a randomized clinical trial, cognitive performance was found to be preserved in Mediterranean diet intervention groups. In a Spanish study, 447 cognitively healthy participants (with a mean age of 67 years) were divided into groups using a Mediterranean diet supplemented with extra virgin olive oil (1 l/week), and a Mediterranean diet supplemented with mixed nuts (30 g/day), or a control diet (advice to reduce dietary fat) [150]. During a median follow-up of 4.1 years, the participants in both Mediterranean diet groups had improved cognitive performance, whereas the control group participants had declined cognitive performance.

Other dietary patterns and specific food items, such as fruits and vegetables, have been studied in relation to cognitive outcomes. The results are contradictory, with

some studies reporting protective effects, others reporting no such associations. For example, two large cohort studies observed no associations between poor dietary habits and cognitive performance or an increased risk of dementia. In the Whitehall II Study, 8,225 participants (with a mean age of 50 at baseline) were followed up for a median of 25 years [151]. In that study, a higher score indicating a healthier diet in a food frequency questionnaire at baseline was found to be not associated with the risk of dementia or cognitive performance, assessed cross-sectionally and longitudinally. In another report from the ARIC study, 13,588 participants (with a mean age of 55 years at baseline) were followed up for 20 years, and their cognitive performance was assessed thrice during the follow-up, and two distinct dietary patterns were identified at baseline [152]. The two dietary patterns included the unhealthy Western dietary pattern, with higher consumption of meats and fried food, and the healthier dietary pattern, with higher consumption of fruits and vegetables. The baseline cognitive performance was found to be poorer in the participants with unhealthy dietary patterns than in the participants with healthy dietary patterns. However, no difference was observed in a 20-year change in cognitive performance or risk of dementia between the groups.

An association between healthy dietary pattern and cognitive performance was observed in the Supplémentation en Vitamines et Minéraux Antioxydant Study, where 3,054 participants (with a mean age of 52 years at baseline) were followed up for an average of 13 years, and their dietary pattern was assessed using a 24-h dietary record for a median of 10 times [153]. In that study, healthy, and traditional dietary patterns were identified. The healthy pattern was observed to be associated with better global cognitive performance and verbal memory compared to the traditional pattern. However, conflicting associations were observed in the Doetinchem Cohort Study, where 2,613 participants (with a mean age of 55 years at baseline) were followed up for five years, and their cognitive performance was assessed twice during the follow-up, and a semi-quantitative food frequency questionnaire was used at baseline to assess their dietary intake during the previous year [154]. A mixed association between different food items and cognitive performance was observed. For example, higher reported vegetable intake was associated with lower information processing speed and worse cognitive flexibility at baseline but with a smaller decline in information processing speed and global cognitive performance. The total intake of fruits, legumes, and juices was not observed to be associated with baseline or change in cognitive performance.

In childhood and adolescence, diet might play a role in determining cognitive performance. In a cross-sectional study with 804 children (with a mean age of 4.2 years) from the Rhea mother–child cohort study in Crete, an unhealthy dietary pattern—including potatoes and other starchy roots, salty snacks, sugar products and eggs—was associated with poorer verbal ability and global cognitive performance

[155]. Furthermore, in a cross-sectional report from the 2010 China Family Panel Studies with 2,029 children and adolescents aged 10 to 15 years, a high-protein dietary pattern was found to be associated with better mathematics test score [156]. That study also observed a conflicting association: a high-fat dietary pattern was associated with better mathematics and vocabulary tests. In addition, a cross-sectional study from the Physical Activity and Nutrition in Children Study with 428 children aged between six and eight years observed an association between poor diet quality—low consumption of fruit and berries, vegetables, high-fiber grain products, and fish and a higher consumption of red meat and sausages—and worse cognitive performance. The association was found to be stronger in boys [157].

In conclusion, the association between dietary habits and cognitive outcomes is somewhat contradictory. The present evidence of an association between nutrition and cognitive outcomes is somehow stronger for healthy dietary patterns, such as the Mediterranean-type diet, compared to individual nutrients and food groups [148] This is suggested possibly because of the cumulative beneficial effects of the many ingredients in these diets. Moreover, dietary habits in childhood may play a role in the development of cognitive performance.

2.4.5.4 Alcohol consumption

Alcohol consumption of >21 units per week in midlife is acknowledged by the Lancet Commission as a risk factor for dementia [3]. In previous studies that examined the associations between different risk factors and cognitive performance, alcohol consumption was often controlled as a covariate in their multivariable models. Prior evidence on alcohol consumption in relation to cognitive performance and the risk of dementia indicates, surprisingly, a nonlinear association. In a French study on a large-scale retrospective cohort of adults (aged ≥20 years) discharged from French hospitals between 2008 and 2013, among all the other risk factors—vascular risk factors, presence of cardiovascular diseases, depression, or low education—heavy drinking in alcohol-use disorders was found to be the strongest modifiable risk factor for dementia onset and, especially, early-onset dementia [158].

In a meta-analysis that summarized 143 studies examining the association between alcohol consumption, cognitive performance, and risk of dementia, heavy alcohol consumption (>3-4 alcohol drinks/day) was found to be associated with an increased risk of dementia and cognitive impairment [159]. However, light to moderate alcohol consumption (≤2 alcohol drinks/day for men and ≤1 alcohol drinks/day for women) was not observed to increase the risk of dementia, cognitive decline, or cognitive impairment. Instead, light to moderate alcohol consumption was associated with a decreased risk of dementia and better cognitive performance but not with cognitive decline. Similar findings were observed in another meta-

analysis of prospective studies, where light to moderate alcohol consumption was associated with a 25% to 28% reduction in any type of dementia [160]. Wine (particularly red) has been shown to have the strongest protective association, whereas beer and spirits have been reported as either unrelated to or related to poor cognitive outcomes [148]. For example, in the Monitoring Project on Cardiovascular Disease Risk Factors study, 1,927 participants aged 56 years were followed up for approximately five years, and their cognitive performance was assessed [146]. Alcohol consumption was found to be associated with faster processing speed and better flexibility among women.

The mechanism for light alcohol consumption's protective association with cognitive outcomes has been hypothesized. It has been suggested that alcohol "protects" by its "preconditioning" effect on neurons and glia, which involves the upregulation of heat shock proteins and other cellular pro-survival mechanisms, such as N-methyl-D-aspartate receptors, protein kinase C epsilon, and focal adhesion kinase [159]. Furthermore, an anti-inflammatory effect may be one mechanism for the protective effect moderate alcohol consumption might have on cardiovascular diseases, thereby reducing the risk of dementia [160]. However, a possible source of bias is suggested to be the sampling effect, according to which the individuals who have higher alcohol consumption may be less likely to participate in cohort studies or attend follow-up studies [160]. Additionally, previous studies did not consider that, though categorized as non-drinkers according to their current drinking habits, those who have never drunk might have different risks than those who quit drinking because of, e.g., a disease.

Moreover, there are no randomized trials on the plausible benefits of light alcohol consumption. Since high alcohol consumption has several adverse health effects, the plausible protective association between alcohol consumption and cognitive outcomes should be cautiously interpreted. This is supported by a previous report from the Whitehall II cohort, where 550 participants (with a mean age of 43 at baseline) were followed up for 30 years, and an MRI was performed after the follow-up [161]. No association between light alcohol consumption and brain structure or even cognitive performance was observed. High alcohol consumption, as expected, was associated with hippocampal atrophy, impaired white matter microstructure, and faster cognitive decline.

2.4.6 Kidney function and serum creatinine

2.4.6.1 Kidney function

Serum creatinine, typically a measure of kidney function, can be used to estimate glomerular filtration rate (eGFR) [162]. The GFR can be estimated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) serum creatinine-based

equation [163]. In the equation, serum creatinine, age, sex, and ethnic background are taken into account, where higher serum creatinine causes a decline in GFR. Typically, eGFR >90 ml/min/1.73m^2 is considered to indicate normal kidney function, but eGFR >60 ml/min/1.73m^2 may also be used as a cut-off point for normal range when measured in subjects without kidney disease or damage [163]. An estimated GFR <60 ml/min/1.73m^2 is considered to indicate chronic kidney disease or kidney damage [163].

There are numerous other means of measuring or assessing GFR. It can also be estimated using the cystatin C-based equation [164]. Moreover, a combination of serum creatinine and cystatin C has been suggested to be more accurate in assessing the associations for end-stage renal disease (eGFR <15 ml/min/1.73m^2) [165]. However, if eGFR is close to the normal level, the CKD-EPI serum creatinine-based equation has been shown to be as accurate as the cystatin C-based equation for estimating GFR [166]. Nevertheless, the CKD-EPI equation still underestimates GFR in healthy populations, failing to detect associations with obesity, higher glucose, or proteinuria [167]. Therefore, the direct measure of GFR reflects kidney function more accurately, and it is measured as creatinine clearance, where the renal clearance of chromium-51 labeled ethylenediamine tetraacetic acid or iothalamate and plasma clearance of chromium-51 labeled ethylenediamine tetraacetic acid or iohexol methods are typically used [168]. Furthermore, other methods and equations to assess GFR have also been used, such as the Modification of Diet in Renal Disease and Cockcroft-Gault serum creatinine-based formulas. In addition to GFR, albuminuria, an accurate sign of glomerular and tubular damage, has been used to assess kidney function [169,170].

Hypertension and diabetes are the main causes of chronic kidney disease and, thereby, low eGFR [171]. Low eGFR is associated with several adverse cardiovascular risk factor levels in blood pressure, BMI, smoking, and physical activity [172]. In a large-scale meta-analysis with over 105,000 participants, eGFR <60 ml/min/1.73m^2 and albuminuria were associated with higher all-cause mortality [173]. Prior evidence on the association between impaired kidney function and poor cognitive performance exists. In a systematic review with participants below the age of 65 years, chronic kidney disease at any stage (diagnosed kidney disease or eGFR <60 ml/min/1.73m^2) was found to be associated with worse cognitive performance [174]. As the review revealed, the lower the eGFR, the higher the number of cognitive domains with poorer performance. Moreover, early-stage chronic kidney disease was found to be associated with worse processing speed, attention, response speed, and short-term memory. Moderate stage chronic kidney disease was found to be associated with poorer executive functioning, verbal fluency, logical memory, orientation, and concentration. Finally, end-stage kidney disease was found to be associated with all the previous cognitive domains, along with cognitive control,

delayed and immediate memory, visuospatial impairment, and overall cognitive impairment. Moreover, in a systematic review and meta-analysis among adults, albuminuria was observed to be associated with an increased risk of cognitive impairment and dementia, worse cognitive performance, and accelerated cognitive decline [169]. In another systematic review and meta-analysis of prospective studies with participants aged ≥45 years, albuminuria was found to be associated with increased risk of cognitive impairment or dementia [175]. However, the association between eGFR <60 ml/min/1.73m^2 and cognitive impairment or dementia produced mixed results, where three studies observed an increased risk of dementia, whereas five studies did not observe any significant association. The overall association between cognitive decline and the risk of dementia was thus nonsignificant.

Furthermore, nonlinear associations of eGFR have been reported. In a large-scale meta-analysis with over 105,000 participants, high eGFR (>105 ml/min/1.73m^2) was associated with increased risk of all-cause mortality. Glomerular hyperfiltration has been suggested as a plausible mechanism for increased GFR [176]. Many studies defined glomerular hyperfiltration using the 95th or 90th percentile of GFR as the cut-off, but other cut-off points have also been used (ranging from 90.7 to 175 ml/min/1.73m^2 [177]. Glomerular hyperfiltration is caused by afferent arteriolar vasodilation as seen in patients with diabetes or after a high-protein meal, or by efferent arteriolar vasoconstriction due to the activation of the renin-angiotensin-aldosterone system [176]. Glomerular hyperfiltration leads to increased GFR, which occurs as an adaptive response to nephron loss, causes glomerular hypertension and, subsequently, glomerulosclerosis, progressive kidney function decline, and initiates glomerular damage [176]. However, since previous studies used both measured GFR and eGFR to define glomerular hyperfiltration, this might have affected the interpretation of the associations, as eGFR has been shown to be associated with an increased number of adverse cardiovascular risk factors compared to measured GFR [172]. The association between eGFR and cardiovascular risk factors may thus be mediated by non-GFR-related factors.

2.4.6.2 Serum creatinine

Non-GFR-related factors on high eGFR levels might indicate a plausible role for low serum creatinine in high eGFR values. Low muscle mass, physical inactivity, and a poor diet are associated with low serum creatinine levels [178]. Creatinine is formed as a result of the nonenzymatic dehydration of muscle creatine [162]. As men have greater muscle mass, and thus greater generation of creatinine than women, sex influence creatinine levels. Furthermore, a higher dietary intake of protein/meat expands the creatine pool and, therefore, an increase in creatinine generation and excretion may be observed [162]. Creatinine is usually produced at a fairly constant

rate and filtered freely by the glomerulus [171]. The additional factors that influence creatinine concentration include tubular secretion, extra-renal excretion, and creatinine degradation [171].

There are a few studies linking high eGFR and low serum creatinine to poor cognitive performance and an increased risk of dementia. Since all the previous studies calculated eGFR based on serum creatinine, they did not extensively assess the non-GFR-related factors. In a large-scale South Korean study with over 2.2 million participants aged ≥45 years (with a mean age of 59 years) and a median follow-up time of 3.1 years, eGFR was calculated using the CKD-EPI serum creatinine-based equation at baseline [179]. In that study, high eGFR (95th percentile) in midlife and old age was observed to be associated with increased all-cause dementia risk in men and women and, specifically, with increased risk of Alzheimer's disease in men.

In two cross-sectional studies from the Tromsø study with over 1,500 participants (with a mean age of 57 years), GFR was estimated using the CKD-EPI serum creatinine-based equation [180] and directly measured as iohexol clearance in midlife [181]. A high eGFR was observed to be associated with worse processing speed, working memory, and associative learning. Moreover, a high measured GFR was observed to be associated with worse performance in the same cognitive domains. However, the association of the measured GFR was found to be diluted after adjusting for education, which might support the different associations between the estimated and measured GFR. In another cross-sectional study from the Reasons for Geographic and Racial Differences in Stroke Study with 23,405 participants (with a mean age of 65 years), chronic kidney disease was found to be associated with impaired cognitive performance in the Six-item Screener that briefly measures recall and temporal orientation [182]. Furthermore, eGFR was calculated using the CKD-EPI serum creatinine-based equation, and eGFR >100 ml/min/1.73m^2 was associated with cognitive impairment. Additionally, in a cross-sectional study of a Brazilian cohort of 246 participants (with a mean age of 74 years), eGFR was calculated using the serum creatinine-based equation [183]. The findings from this study indicated that eGFR <60 ml/min/1.73m^2 and an eGFR >90 ml/min/1.73m^2 were associated with worse performance in the MMSE, i.e., global cognitive performance.

Potential mechanisms

The suggested association of high eGFR, and thus low serum creatinine, with cognitive performance may indicate the potential role of serum creatinine as a non-GFR-related factor in the pathophysiology of cognitive decline. A study examining the cerebral metabolic alterations in Alzheimer's disease found that Alzheimer's

disease patients (N = 40) had higher creatinine concentration in their cerebrospinal fluid compared to the control subjects (N = 34) [184], although no difference was observed in the serum creatinine concentration between the patients and controls. The authors of that study argued that higher concentrations of creatinine in the cerebrospinal fluid observed in the Alzheimer's disease patients may be a result of excessive phosphocreatine usage and/or disrupted creatine-phosphocreatine shuttle that leads to non-enzymatical and irreversible degradation of both phosphocreatine and creatine into creatinine [185]. Based on a negative correlation between creatine and creatinine in both serum and cerebrospinal fluid in Alzheimer's disease patients, it was hypothesized that creatinine is produced at the expense of creatine in conditions of inadequate glucose supply [184]. Additionally, because of the observed negative correlation of creatinine with the blood–brain barrier permeability, it was suggested that the creatinine-related process takes place in the central nervous system. Therefore, it might be speculated that a high systemic concentration of creatine and creatinine may be beneficial for preserving energy metabolism in the brain. However, with the lack of experimental data elucidating these mechanistic aspects, the detailed pathophysiology explaining the link between serum creatinine and cognitive performance remains unclear.

In addition to non-GFR-related factors, glomerular hyperfiltration might still be a potential link between serum creatinine and cognitive performance. However, only a few studies have introduced glomerular hyperfiltration as a potential mechanism for increased eGFR [179,183] or measured GFR [181]. Glomerular hyperfiltration is linked to the renin-angiotensin-aldosterone system activation [176] and high renal generation as well as low systemic bioactivity of nitric oxide [186]. These factors play a role in endothelial dysfunction [23]. Both endothelial dysfunction and low nitric oxide bioactivity play a role in age-related cognitive decline, where vascular structure and function are comprised, which eventually might lead to cerebral hypoperfusion [23]. Furthermore, glomerular hyperfiltration might be linked to the vascular mechanisms for cognitive deficits, as increased arterial stiffness [187] and coronary artery calcification [188] were observed in participants with glomerular hyperfiltration (which, however, was defined using eGFR based on serum creatinine in both studies). Also, subclinical cardiovascular disease markers—such as carotid atherosclerosis and electrocardiographic signs of left ventricular hypertrophy—have been found to be associated with increased measured GFR [189].

Adverse cardiovascular risk factor levels might also be behind the association between high GFR, low serum creatinine, and poor cognitive performance. Thus, low serum creatinine or high GFR might indicate an adverse cardiovascular risk factor profile, which is thus associated with poor cognitive performance. For example, high physical activity and a favorable diet are shown to be associated with better cognitive performance [95]; importantly, these factors are also associated with

higher serum creatinine [178]. Additionally, several previous studies have shown that other adverse cardiovascular risk factors are linked to high GFR and, thus, low serum creatinine. For example, in the Kansai Healthcare Study, 10,118 men aged 40 to 55 years were followed up for six years, and their GFR was estimated using the Modification of Diet in Renal Disease equation for the Japanese serum creatinine-based equation, and proteinuria was assessed using a standard dipstick [190]. It was observed that smoking is associated with high eGFR (≥117 ml/min/1.73m^2) and proteinuria. Moreover, in a cross-sectional study of 1,572 healthy men (with a mean age of 18 years), creatinine clearance was estimated using the Cockcroft-Gault serum creatinine-based equation indicating GFR [191]. Glomerular hyperfiltration was defined as eGFR over the mean +2 standard deviation (SD), and the participants in that group were observed to have more accumulated metabolic risk factors, including overweight, elevated blood pressure, and low HDL cholesterol.

Diabetes and prediabetes have been shown to be associated with low serum creatinine/high GFR. In a cross-sectional study with 8,643 adolescent participants (aged between 12 and 17 years), eGFR was calculated using the Chronic Kidney Disease in Children serum creatinine-based equation [192]. Glomerular hyperfiltration was defined as eGFR ≥120 ml/min/1.73m^2, and the participants in that group were observed to have higher triglyceride, insulin, and insulin resistance. In another cross-sectional study from the Tromsø study in 1,560 participants (mean of age 58 years), GFR was measured using plasma iohexol clearance, and high GFR was defined as the 90th percentile [193]. Among the participants without diabetes, high measured GFR was associated with impaired fasting glucose and HbA1c levels. No association was observed for fasting insulin levels. Furthermore, in a large-scale cross-sectional study of 99,140 participants (with a mean age of 52 years and age between 20 and 89 years), eGFR was calculated using the Modification of Diet in Renal Disease serum creatinine-based equation, and glomerular hyperfiltration was defined as the 95th percentile [194]. The findings from that study indicated that prediabetes, diabetes, prehypertension, and hypertension were associated with high eGFR, thus plausibly indicating glomerular hyperfiltration.

Obesity or adiposity has been suggested to be linked with low serum creatinine/high GFR. In a cross-sectional study of 5,493 US adolescents and adults (age range between 12 and 29 years), eGFR was calculated using the CKD-EPI serum creatinine-based equation for participants ≥18 years, and the Chronic Kidney Disease in Children equation for participants <18 years, and increased eGFR was defined as the 95th percentile [195]. Both a higher BMI and diabetes were found to be associated with increased eGFR. Also, in a cross-sectional study of 301 middle-aged African Americans (with a mean age of 45 years), GFR was measured using inulin and para-aminohippurate clearances [196]. Increased GFR, defined as ≥140 ml/min, was observed to be associated with higher BMI levels in age, sex, blood

pressure, fasting glucose, and urinary sodium excretion. Additionally, in a cross-sectional study of 6,902 Chinese participants (with a mean age of 39 years), adiposity was measured using biological impedance, and eGFR was calculated using the CKD-EPI serum creatinine-based equation [197]. The participants were divided into quartiles according to their eGFR. The participants in the upper eGFR quartile were observed to have higher fat and lean body mass ratio, indicating higher adiposity. However, no association was observed for BMI.

Previous studies have also shown that low serum creatinine/high GFR is associated with adverse cardiovascular end points. In the CARTaGENE population cohort, 9,515 participants with a mean age of 50 years and without hypertension, diabetes, cardiovascular disease, chronic kidney disease, or statin/aspirin use were followed up for a median of 5.8 years, and their eGFR was calculated using the CKD-EPI serum creatinine-based equation [198]. In that study, glomerular hyperfiltration was defined as the 95th percentile, and the participants in the hyperfiltration group were observed to have a greater risk of adverse cardiovascular events (cardiovascular mortality, myocardial infarction, unstable angina, heart failure, stroke, or transient ischemic attack). Moreover, in a cross-sectional study of 8,941 participants (with a mean age of 62 years) with atherosclerotic vascular disease, GFR was estimated using the Modification of Diet in Renal Disease and Cockcroft-Gault serum creatinine-based formulas [199]. An estimated GFR $\geq$125 ml/min/1.73m^2 predicted risk of death, congestive heart failure, myocardial infarction, and stroke.

In conclusion, low serum creatinine and high GFR may indicate the early manifestation of risk factors, such as elevated blood pressure, prediabetes, obesity, adiposity, and smoking. These early adverse cardiovascular risk factors, it could be speculated, are accumulated in individuals with low serum creatinine before the factors result in the clinical manifestation of adverse cardiovascular risk factor levels and exceed the recommended guidelines. It is important to note that many of these adverse cardiovascular risk factors are associated with poor cognitive performance. However, only a limited number of studies have examined this association in young populations. Based on the evidence from previous studies, it may be hypothesized that low serum creatinine and high GFR may influence cardiovascular risk factors from childhood and is thus linked to adulthood cognitive performance.

2.5 Dementia prevention

The aging population and, thereby, the increasing prevalence of cognitive deficits highlight the need for risk reduction as a crucial target on the global public health agenda. The Lancet Commission on Dementia Prevention, Intervention, and Care proposed that a 40% reduction in the prevalence of dementia would be achieved if 12 different lifestyle or environmental risk factors are eliminated across the lifespan [3].

Observational studies have identified several potentially modifiable risk factors for cognitive decline and dementia. Whether the risk factors determine cognitive health from childhood or only later in adulthood is uncertain. However, no prospective observational study has comprehensive data from childhood to old age to systematically assess the associations of the risk factors across different age windows on cognitive decline or dementia in old age. Moreover, no firm conclusions on causal relationships can be drawn from observational studies. Therefore, it is also crucial to conduct randomized clinical trials to examine the effects of interventions on risk factors to reduce the risk of cognitive decline and dementia. Most of the previous preventive interventions have been tested in small groups, and usually only a single lifestyle risk factor was targeted during the intervention [200]. These trials yielded either negative or modest results.

However, larger randomized trials have also been conducted. Multidomain interventions that targeted several risk factors and mechanisms simultaneously were used in these trials. In the FINGER double-blind randomized controlled trial, 1,260 participants aged 60 to 77 years were divided into a 2-year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring) or a control group (general health advice) [201]. In this trial, intervention on several cardiovascular risk factors was found to be associated with overall cognitive performance in tests measuring executive function and processing speed as well as improved cardiovascular risk factor levels in BMI, dietary habits, and physical activity. However, in two other large (N = 1,680, and N = 3,526) randomized trials among old-aged participants on several cardiovascular risk factors, no significant association between intervention and cognitive performance was observed [200].

The future direction in dementia prevention aims at large-scale multidomain lifestyle intervention. In 2017, the World-Wide FINGER was launched and, currently, over 40 countries are participating [202]. Its main goal is to reduce the risk of cognitive decline from at-risk asymptomatic stages to early symptomatic stages. However, significant attention has been given to the primary prevention of dementia by treating risk factors in midlife or later. It is important to note that observational studies have recently found that the roots of cognitive performance begin possibly in early life or even in childhood. As the neuropathological disease process in cognitive deficits is known to begin several years or decades before any symptoms [13], middle-aged or elderly populations are not necessarily the optimal target populations when aiming to find the means for the primary or primordial prevention of cognitive deficits.

Having a higher cognitive reserve has been suggested to provide preventive aspects against cognitive deficits [3]. In individuals with higher cognitive reserve, it is suggested that early life factors, such as education and leisure activity, may prevent, or at least postpone, age-associated cognitive decline. These factors should

thus be the focus of preventive means. The cognitive reserve hypothesis posits that some individuals have a greater ability to withstand pathologic changes to the brain, such as accumulation of amyloid protein, as a result of having a greater brain reserve [15]. Higher levels of education, participation in leisure activities, higher SES, and baseline intelligence might thus protect against the clinical manifestations of brain disease [15]. Furthermore, reducing neuropathological damage—such as amyloid or tau-mediated, vascular or inflammatory—by treating other plausible risk factors is another possible mechanism for dementia prevention [3]. These other risk factors include cardiovascular and lifestyle risk factors. Reducing adverse cardiovascular risk factors or an unfavorable lifestyle early enough during one's life-course might thus be paramount in cognitive deficit prevention.

2.6 Summary of the literature review

According to the previous literature, several risk factors are related to cognitive performance and the risk of dementia. Risk factor reduction may offer plausible means for the primary and primordial prevention of cognitive deficits or dementias. Delaying the onset of cognitive impairment and dementias by only a few years could substantially reduce their prevalence and the concomitant human and economic burden [202].

Previous studies have presented substantial evidence for the association of adverse risk factor levels in midlife on cognitive performance. These adverse risk factors include health factors, such as elevated blood pressure, high total cholesterol, overweight and obesity, diabetes and impaired fasting glucose, cardiovascular risk factor accumulation, chronic kidney disease, and serum creatinine. The adverse risk factors also include behavioral factors, such as low physical activity, smoking, alcohol consumption, and poor dietary habits. However, it is not possible to evaluate causal relations based on observational studies. Previous experimental evidence supports a sufficient causal relation at least between cognitive performance and elevated blood pressure, high total cholesterol, overweight and obesity, and physical activity. However, the causal relation especially between serum creatinine and cognitive performance is uncertain.

It is important to note that evidence of early life adverse risk factor levels on later life cognitive performance has started to increase recently. Previously, the lack of this evidence was largely due to missing observational cohorts since early life. The CARDIA study sheds light on the associations between early adulthood risk factor levels and midlife cognitive performance. However, recent observations from the Young Finns Study indicate that the roots of adulthood cognitive performance may be in childhood. In particular, cardiovascular risk factor accumulation might have an important role in cognitive health. However, research on cardiovascular risk factor

accumulation since childhood is scarce. Additionally, the early manifestation of risk factors, such as elevated blood pressure, obesity, and diabetes, and their accumulation before becoming clinically apparent might indicate the importance of primordial prevention of risk factors.

Therefore, as part of the Young Finns Study, this thesis has major advantages in fulfilling the gaps of knowledge in previous literature. Its unique prospective design, which covers childhood, adolescence, and midlife, offers research possibilities to study the early life and adulthood adverse risk factor levels in relation to early midlife cognitive performance.

3 Aims

This study's overarching objective was to underline the so far indistinct longitudinal associations between cardiovascular risk factors since childhood and cognitive performance in a healthy middle-aged population. To elucidate the determinants for midlife cognitive performance and to underline the importance of early identification of cardiovascular risk factors for adulthood cognitive health, this study aimed A) to provide novel evidence on the associations of physical activity, blood pressure, serum lipids, BMI, and serum creatinine levels with cognitive performance in midlife, and B) to highlight the harmful associations of cardiovascular risk factor accumulation since childhood with cognitive performance in midlife.

The following are the specific aims of the study:

I. to investigate the longitudinal associations of physical activity accumulation since childhood with cognitive performance in midlife.
II. to study the longitudinal associations of specific cardiovascular risk factors and their accumulation since childhood with cognitive performance in midlife.
III. to study the longitudinal associations of clinically normal serum creatinine in adulthood with cognitive performance in midlife.

4 Materials and Methods

4.1 The Cardiovascular Risk in Young Finns Study

The Cardiovascular Risk in Young Finns Study is a national ongoing multicenter longitudinal population-based study focusing on cardiovascular risk factors from childhood to adulthood [203]. The original aim of the Young Finns Study was to assess the risk factors underlying cardiovascular diseases from childhood to adulthood. The first cross-sectional study was conducted in five Finnish university cities with medical schools (Turku, Tampere, Helsinki, Kuopio, and Oulu) and their rural surroundings in 1980. A total of 4,320 Finnish children and adolescents aged 3, 6, 9, 12, 15, and 18 years were randomly selected from the national population register, of which 3,596 (83.2%) participated in the clinical examinations (49% male). The follow-up studies were conducted for the whole study population in 1983, 1986, 2001, 2007, and 2011, and for a subsample in 1989 and 1992 (Table 2).

Table 2. The study design and participation rates (%) at each stage of the Young Finns Study.

Year	N	%	Age cohorts																	
1989	3,596	100	3	6	9	12	15	18												
1983	2,991	83		6	9	12	15	18	21											
1986	2,779	77			9	12	15	18	21	24										
1989*	632					12	15	18	21	24	27									
1992*	891						15	18	21	24	27	30								
2001	2,284	63								24	27	30	33	36	39					
2007	2,204	61										30	33	36	39	42	45			
2011	2,062	57												34	37	40	43	46	49	

*Limitations in the sampling size in 1989 and 1992 do not imply voluntary non-participation. In 1989, physical examinations and blood tests were gathered only in one centre (Turku). In 1992, the limitation in the sampling size was due to economic constraints. The table has been adapted and modified from the work of Raitakari et. al. (2008); Cohort Profile: The Cardiovascular Risk in Young Finns Study [203] with permission Oxford University Press.

4.2 Study design

In this thesis, study I aimed to investigate the independent associations of cumulative exposure to physical activity in childhood (six to 12 years of age), adolescence (12 to 18 years of age), young adulthood (18 to 24 years of age), and adulthood (24 to 37 years) with cognitive performance in midlife. The longitudinal analyses for physical activity included 2,026 participants who had data on cognitive performance in midlife.

Study II aimed to identify the trajectories of blood pressure, serum lipids, and BMI from childhood (nine years of age) to midlife (49 years of age) and to study the association of individual risk factors as well as cardiovascular risk factor accumulation with cognitive performance in midlife. The longitudinal analyses for cardiovascular risk factors included 2,339 to 2,562 participants who had data on blood pressure, serum lipids, and BMI from childhood to midlife. Of these, 2,026 participants had data on cognitive performance in midlife.

Study III aimed to identify the trajectories of clinically normal serum creatinine from young adulthood (24 years of age) to midlife (49 years of age) and to study the role of low serum creatinine on the cardiovascular risk factor profile and on cognitive performance in midlife. The longitudinal analyses for serum creatinine included 2,177 participants who had data from at least two follow-up studies in adulthood. Of these, 2,026 participants had data on cognitive performance in midlife.

4.3 Cognitive performance

During the latest follow-up examination in 2011, the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, United Kingdom) was used to assess the cognitive performance of participants aged 34 to 49 years (N = 2,026) [18]. The CANTAB® is a computerized, predominantly nonlinguistic, and culturally neutral test focusing on a wide range of cognitive domains. It is performed using a validated touchscreen computer system. The full test battery includes 24 individual tests, from which a suitable test battery for each particular study may be selected. In the Young Finns Study, the test battery was selected so that it could be accomplished in 20 to 30 minutes and that it included tests sensitive to aging [204,205]. The tests in the Young Finns Study measured several cognitive domains: (a) short-term memory, (b) spatial working memory, (c) problem solving, (d) reaction time, (e) attention, (f) rapid visual processing, (g) visual memory, (h) episodic memory, and (i) visuospatial learning.

Cognitive testing was performed during the clinical examination. Due to the blood sampling included in the study protocol, the subjects came to the examinations after fasting for at least 12 hours. They were instructed to avoid smoking and heavy physical activity as well as to avoid drinking alcohol and coffee during the previous

evening and the morning before the examinations. Before cognitive testing, the subjects were provided with a light snack, including a whole grain oat-based snack biscuit, a small portion of fruit or berry oatmeal, and weak fruit or berry juice.

During cognitive testing, a motor screening test, measuring psychomotor speed and accuracy, was conducted first. In this study, the motor screening test was considered a training procedure in which the participants were introduced to the equipment used in the testing and a screening tool to point out any difficulties in vision, movement, comprehension, or their ability to follow simple instructions. During the motor screening test, a series of red crosses were shown in different locations on the screen, and the participants were advised to touch, as quickly as possible, the center of the cross every time it appeared.

The Paired Associates Learning (PAL) test was used to assess visual and episodic memory as well as visuospatial associative learning, containing aspects of both delayed-response procedure and conditional learning. During the PAL test, one, two, three, six, or eight patterns were displayed sequentially in boxes placed on the screen. After, the patterns were presented at the center of the screen, and the participants were supposed to point to the box in which the particular pattern was previously seen. The test moves on to the next stage if all the patterns are placed in the right boxes. In the case of an incorrect response, all the patterns are redisplayed at their original locations, and another recall phase is followed. The test is terminated if the patterns are still incorrectly placed after 10 presentation and recall phases.

The Spatial Working Memory (SWM) test was used to measure the participants' ability to retain spatial information and manipulate the items stored in their working memory, problem solving, and the ability to conduct a self-organized search strategy. During this test, the participants were presented with randomly distributed colored boxes ranging in number from four to eight. After, the participants were supposed to search for tokens hidden in the boxes. When a token was found, it was supposed to be moved to fill an empty panel on the right-hand side of the screen. Once the token was moved from the box, the participant had to recall that the computer would never hide a new token in a box that previously contained one; therefore, the participants were not supposed to revisit the same boxes again.

The Reaction Time (RTI) test assessed the participants' speed of response and movement on tasks where the stimulus was either predictable (a simple location task) or unpredictable (a five-choice location task). In the first part of this test, a large circle was presented at the center of the screen, and the participants were supposed to press a button on a press pad until a small yellow spot appeared in the large circle. When the yellow spot appeared, the participants were supposed to touch the spot as soon as possible with the same hand that was pressing the button on the press pad. In the second part of the test, the same task was performed, except that, in this part, five large circles were presented on the screen, and the small yellow spot could

appear in any of the five circles. Again, the participant was supposed to touch, as soon as possible, the yellow spot with the hand pressing the button on the press pad.

The Rapid Visual Information (RVP) test was used to assess visual processing, recognition, and sustained attention. In this test, the participants were presented with a number sequence (e.g., 3, 5, 7) next to a large box, where numbers appeared in a random order. Whenever a particular sequence was presented, the participants were supposed to press a button on a press pad. At the beginning, the participants were given visual cues (i.e., colored or underlined numbers) to help them recognize the particular sequence. The cues were removed as the test progressed.

Each of the CANTAB® tests produced several variables. To reduce the number of variables and identify the components accounting for the majority of the variation in the cognition dataset, principal component analysis was conducted. It was selected because it allows the identification of the main sources of variation in multidimensional data without losing important information and without introducing inherent bias due to subjectivity. For all tests, principal component analyses were performed separately. The first components resulting from these analyses were considered to represent cognitive performance related to a particular domain. After creating the overall and test-wise principal components, their distributions were analyzed. The component for the motor screening test was excluded from further analyses because it did not discriminate between the subjects, indicating a ceiling effect. All the other components were normalized based on the rank order normalization procedure, resulting in four separate variables, each with a mean value of zero and a SD of one. After, the principal components were transformed so that a greater value in the principal component indicates better cognitive performance (for example, a higher value in the component for reaction time indicates better performance, not a longer reaction time). All the available data for each cognitive test were used in the analyses, and therefore, the number of participants varied between the models (177 were excluded due to technical reasons; 51 refused to participate in all or some of the tests).

4.4 Physical examination

Physical examination was included in all follow-up studies. Blood pressure was measured from the right-side brachial artery with a standard mercury sphygmomanometer in 1980 and 1983 and a random zero sphygmomanometer (Hawksley & Sons Ltd.; Lancing, UK) in 1986, 1989, 1992, 2001, 2007, and 2011 follow-ups in a sitting position after five minutes of rest. Korotkoff's fifth phase was used as the sign of diastolic blood pressure and the first phase as the sign of systolic blood pressure. Readings to the nearest even number of millimeters of mercury were performed at least thrice on each subject. The average of these

measurements was used in the analysis. Weight was measured in light clothes without shoes with a digital scale, with an accuracy of 0.1 kg, and height was measured with a wall-mounted stadiometer (Karhu, Finland) with 0.5 cm accuracy. BMI was calculated as weight (kg) / height (m^2).

4.5 Questionnaires

The annual gross income was considered an indicator of SES in childhood [206]. The participants' parents reported the annual income of the family in childhood at the baseline examination in 1980. Four annual family income strata at the time of baseline were determined and converted into their present-day value: 1) <17,000 Euros; 2) 17,000–27,000 Euros; 3) 27,001–34,000 Euros; 4) >34,000 Euros.

Adulthood education is considered an indicator of SES in adulthood. Education was queried in follow-up studies in 2001, 2007, and 2011. The maximum years of education was determined as a continuous variable from self-reported data concerning the total years of education attained until 2011.

Childhood school performance was considered a proxy for childhood cognitive ability. School performance, expressed as grade point average (i.e., the mean grade of all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline), was also queried.

Cigarette smoking was ascertained as part of a self-administered questionnaire throughout the follow-up studies among participants aged 12 years and older. Data on smoking status were dichotomized into smokers and nonsmokers. Those who reported having a smoking habit at any of the follow-up phases at the ages between 12 and 24 years were classified as early life smokers. Those who reported current smoking in any of the adulthood follow-up studies (2001, 2007, or 2011) were classified as adulthood smokers.

Dietary habits were assessed in adulthood follow-up studies with a detailed quantitative food frequency questionnaire that provided an estimate of food consumption in grams per day [207]. The intake goals defined by the AHA [94] was used and are expressed for a 2000-kcal diet. Therefore, the intake goals according to the participants' total energy intake were scaled. Then, the achievement of the five AHA ideal dietary goals was dichotomized: ≥450 grams per day of fruits and vegetables, ≥2 100g servings per week of fish, ≥3 30g servings per day of whole grain rye bread, sodium <1500 mg/d, and ≤450 kcal of sugar-sweetened beverages per week. A diet score (ranging from zero to five points) was calculated based on the number of ideal dietary goals achieved.

In the follow-up studies in 2001, 2007, and 2011, data on antihypertensive and dyslipidemia medication use were obtained from questionnaires. There were no

participants that used antihypertensive or dyslipidemia medications in childhood but not in adulthood.

4.6 Physical activity

Physical activity was measured with a standardized self-administered questionnaire in all the study phases from the age of nine (Tables 3 and 4) and with a questionnaire administered by the parents for participants aged between three and six years (Table 5). Between 1980 and 1989, the questionnaire included questions concerning the participants' frequency and intensity of leisure-time physical activity, participation in sports-club training, participation in sport competitions, and habitual way of spending leisure time (Table 3 shows the questions assessing physical activity and the creation of the physical activity index (PAI) between 1980 and 1989). Participation in sports competitions was dichotomized (no = 1 and yes = 2), while all the other items were recoded from inactivity or very low activity (1) to regular or vigorous activity (3). Subsequently, the sum of all the items was calculated to form a PAI with scores ranging from five to 14 [208]. In the follow-ups from 1992 onward, the physical activity questionnaire comprised items on the frequency and intensity of physical activity, frequency of vigorous physical activity, hours spent on vigorous physical activity, average duration of a physical activity session, and participation in organized physical activity (Table 4 shows the questions assessing physical activity and the creation of the PAI between 1992 and 2011). Similar to previous data, each item was recoded from one to three, and the sum of the items was again calculated as the PAI, with scores ranging from five to 15 [208]. The validation of the physical activity data has been done in previous Young Finns Study studies [208–210]. The results from the validation analyses indicate that the Young Finns Study physical activity questionnaire is an acceptably valid subjective measure of physical activity, as there was a significant moderate correlation between PAI and the average number of daily pedometer steps (correlation coefficients 0.25–0.31) [209] even though the pedometer does not measure all the possible aspects of physical activity, such as swimming and cycling. The reliability analyses conducted on the Young Finns Study physical activity questionnaire data showed significant correlations that varied between 0.44 and 0.69 among females, and between 0.49 and 0.76 among males in 1980 [208]. Similarly, in 2001, the significant correlations varied between 0.59 and 0.85 among females, and between 0.74 and 0.85 among males [208]. In addition, a metabolic equivalent index was calculated from the product of intensity * frequency * duration and commuting physical activity [210].

Table 3. The assessment of physical activity and creation of the physical activity index (PAI) in 1980–1989.

Question in the questionnaire	Code for PAI
How often do you engage in leisure-time physical activity at least half an hour per time?	
Not at all	1
Less than once a month	1
Once a month	1
2–3 times a month	1
Once a week	2
Once a week 2–6 times a week	2
Every day	3
How much are you breath-taking and sweating when you engage in physical activity and sport?	
Not at all	1
Moderately	2
A lot of	3
How many times a week do you usually engage in the training sessions of sports clubs?	
Not at all	1
Occasionally	1
Less than once a month	1
Once a month or more	2
Once a week	2
Many hours and times a week	3
Do you participate in regional or sports clubs level competitions?	
No	1
Yes	2
What do you usually do in your leisure time?	
I am usually indoors and read or do something like that	1
I spend my time indoors and outdoors, outdoors I usually walk or spend time with my friends	2
I am usually outdoors and exercise rather much	3
PAI TOTAL, range	5–14

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Table 4. The assessment of physical activity and creation of the physical activity index (PAI) in 1992–2011

Question in the questionnaire	Code for PAI
How much are you breath-taking and sweating when you engage in physical activity and sport?	
Not at all	1
Moderately	2
A lot of	3
How often do you engage in intensive physical activity?	
Not at all	1
Once a month or more	1
Once a week	2
2-3 times a week	2
4-6 times a week	2
Every day	3
How many hours a week do you engage in intensive physical activity?	
Not at all	1
Hour a week	1
1 hour a week	1
2–3 hours a week	2
4–6 hours a week	2
Over 7 hours a week	3
How long time do you usually spend for physical activity?	
Less than 20 min	1
20–40 min	2
40–60 min	2
More than 60 min	3
Do you participate in organized physical activity?	
Not at all	1
Occasionally	1
Regularly about once a week	2
Many hours and times a week	3
PAI TOTAL, range	5–15

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Table 5. The assessment of physical activity and creation of the physical activity index (PAI) in 1980–1983 among 3- and 6-year-old participants

Question in the questionnaire	Code for PAI
How many hours does your child spend time playing outdoor daily in winter?	
1–2	1
3–4	2
≥5	3
How many hours does your child spend time playing outdoor daily in summer?	
1–5	1
6–7	1
≥8	2
How physically active your child is while playing outdoors compared to other children?	
Much less active	1
Less active	1
Similarly active	2
More active	3
Much more active	3
Does your child play such vigorously that playing makes him/her to sweat or to feel breathlessness?	
Never	1
Sometimes	2
Quite often	3
Almost always	3
Does your child enjoy playing mostly?	
Indoors	1
Outdoors	2
As much both	3
How is your child compared to other children?	
Inactive	1
Sometimes active / sometimes inactive	2
Lively and active	3

Is your child interested or has he/she been encouraged to participate in physical activity or sport?	
No	1
Yes	2
What kind of activities does your child participate? *	
0	1
1	2
2-6	3
PAI TOTAL, range	5–15

* Parents reported freely three activities that the child participated most often. The activities were coded (1 or 2) according to their strenuousness. The number of strenuous activities was used to define the points given to the child on this question. Reproduced from the original publication I in the Medicine and Science in Sports and Exercise with permission of Wolters Kluwer Health, Inc.

4.7 Genetic analyses

Genotyping was performed for 2,443 participants using a custom build Illumina Human 670k BeadChip at the Welcome Trust Sanger Institute. The genotypes were called using the Illuminus clustering algorithm [211]. The genotype imputation was done using the Beagle software [212] and the Sequencing Initiative Suomi as reference data. A polygenic risk score for cognitive performance (hereafter polygenic risk score) was calculated using LDpred, a Bayesian method that estimates posterior mean causal effect sizes from genome-wide association study summary statistics by assuming a prior for the genetic architecture and linkage disequilibrium information from a reference panel [213]: an infinitesimal fraction of the causal variants was assumed, and the summary statistics from Savage et al. [214] genome-wide association study for intelligence were used. The linkage disequilibrium between the markers was estimated from the Sequencing Initiative Suomi data. The polygenic risk score was used as a proxy for childhood cognitive performance in Study II.

APOE alleles (ε2, ε3, ε4) were determined based on single nucleotide polymorphisms (SNPs) rs7412 and rs429358 haplotypes [215]. Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Minikit and automated biorobot M48 extraction (Qiagen, Hilden, Germany). Genotyping was performed using the Taqman SNP Genotyping Assays (C__904973_10, C_3084793_20) and the ABI Prism 7900 HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA). For quality control, water controls, random duplicates, and known control samples were run in parallel with unknown DNA.

4.8 Biochemical analyses

Venous samples were drawn from the right antecubital vein after a 12-h overnight fast. In 1980, an aliquot for serum lipid analyses was stored at -25°C until analysis. All the lipid determinations were done in duplicate and in the same laboratory. The total cholesterol concentrations were measured using a fully enzymatic CHOD-PAP method (Boehringer Mannheim, Mannheim, Germany) with OLLI 3000 and Kone CD analyzers (Kone Co., Espoo, Finland). In 1980, serum high-density lipoprotein (HDL) cholesterol concentrations were measured from the supernatant after precipitation of very low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein (LDL) particles with dextran sulphate-MgCl2 (Pharmacia, Uppsala, Sweden). All the analyses were performed as simultaneously as possible in the laboratory of the Rehabilitation Centre of the Social Insurance Institution, Turku, Finland. The LDL cholesterol concentration was calculated using the Friedewald formula [216] for participants with triglycerides <4 mmol/l.

In the adulthood follow-ups conducted in 2001, 2007, and 2011, serum or plasma was separated and stored at -70 °C until analysis. In 2001, all the analyses were performed in the laboratory of the Research and Development Unit of the Social Insurance Institution, and in 2007 and in 2011 in the laboratory for the Population Research of the National Institute for Health and Welfare, Turku. The serum total cholesterol and triglyceride concentrations were determined enzymatically (Olympus System Reagent; Olympus Diagnostica GmbH, Hamburg, Germany) in a clinical chemistry analyzer (AU400; Olympus Optical Ltd, Mishima, Japan). HDL cholesterol was analyzed after the precipitation of very low-density lipoprotein cholesterol and LDL cholesterol with dextran sulphate-$MgCl_2$. The concentration of LDL cholesterol was calculated using the Friedewald formula [216] for participants with triglycerides <4 mmol/l. Because of the changes in determination methods and kits across the study years, the lipid levels from 1980 and triglycerides from 2007 were corrected using correction factor equations to correspond with the samples taken in 2001 [217]. No correction equations were needed for the 2007 and 2011 total cholesterol, LDL cholesterol, and HDL cholesterol values.

Serum creatinine was determined spectrophotometrically (Creatinine reagent, Olympus, Ireland) on an AU400 analyzer (Olympus, Japan) in three follow-up studies during adulthood and midlife (2001, 2007, and 2011). GFR was estimated using the CKD-EPI serum creatinine-based equation [163].

In 1980, serum insulin was measured by modifying the immunoassay method of Herbert et al. [218]. In 2001, 2007, and 2011, serum insulin was measured using the microparticle enzyme immunoassay kit (Abbott Laboratories, Diagnostic Division, Dainabot, Japan). The serum glucose concentrations were determined by the enzymatic hexokinase method (Glucose System Reagent, Beckman Coulter Biomedical O'Callaghan's Mills, Ireland) on an automatic analyzer (AU400,

Olympus, Tokyo, Japan). Due to changes in methods or reagents between 2001 and 2007, the glucose levels in 2007 were corrected to the 2001 levels: (glucose (2007)-0.0235)/0.9471).

The concentration of glycated hemoglobin (HbA1c) was assayed with an immunoturbidimetric method (Hemoglobin A1c assay, Abbot, USA) on an Architect ci8200 analyzer (Abbott) [219]. Insulin resistance and sensitivity was estimated using the Homeostatic Model Assessment of Insulin Resistance formula, which was calculated as fasting insulin (mU/l) multiplied by fasting glucose (mmol/l) divided by 22.5.

4.9 Definition and assessment of impaired fasting glucose and type 2 diabetes

The classification of impaired fasting glucose and type 2 diabetes was based on the criteria defined by the WHO [85]. The participants were classified as having impaired fasting glucose if they had fasting serum glucose >6 mmol/l to <7 mmol/l. They were classified as having type 2 diabetes if they had a fasting serum glucose ≥ 7.0 mmol/l, had an HbA1c level of ≥48 mmol/mol (≥6.5%), reported receiving oral hypoglycemic agents and / or insulin injections, and did not have type 1 diabetes or reported a diagnosis made by a physician. Furthermore, the diagnoses of type 2 diabetes were obtained from the questionnaires and register data. Data on the diagnosis of type 1 diabetes were assessed by a self-report questionnaire.

4.10 Ethics

The Young Finns Study was approved by the 1st ethical committee of the Hospital District of Southwest Finland and by local ethical committees (1st Ethical Committee of the Hospital District of Southwest Finland, Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital, Helsinki University Hospital Ethical Committee of Medicine, The Research Ethics Committee of the Northern Savo Hospital District and Ethics Committee of the Northern Ostrobothnia Hospital District) [215]. The study protocol of each study phase corresponded to the WHO proposal. All the present subjects gave written informed consent, and the study was conducted in accordance with the Helsinki Declaration. At prior follow-ups of the Young Finns Study, informed consent of every participant under the age of 18 was obtained from a parent and / or legal guardian.

4.11 Statistical analyses

All the statistical analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, North Carolina, USA). A 2-tailed P-value < 0.05 was considered the level of statistical significance. The Wilcoxon rank sum test and the χ^2-test were used to study the differences between the participants and non-participants in age and sex. Due to significant differences in age and sex, all the other analyses were adjusted for age and sex. Linear regression models were used for continuous variables, and logistic regression for binary variables. The values of serum triglycerides were $\log_{10}$ transformed before analyses due to skewed distributions.

In studies II and III, to identify the subgroups of the Young Finns Study participants who shared similar underlying trajectories between nine and 49 years of age and in serum creatinine between 24 and 49 years of age, the heterogeneity in the longitudinal development of systolic and diastolic blood pressure, serum lipids, BMI, and serum creatinine was investigated using the group-based trajectory modeling performed with the SAS PROC TRAJ procedure [220]. The PROC TRAJ procedure uses the maximum likelihood estimation method, which handles incomplete data without listwise deletion. The diagnostics of model accuracy for each risk factor was based on standard criteria [221], which are the Bayesian Information Criterion (BIC), indicating the models' goodness of fit, and the posterior probability, indicating internal reliability. The BIC values were compared with the preceding simpler models (fewer amount of trajectory groups or lower term), and $2*\Delta BIC > 10$ was considered a significant change indicating better goodness of fit. Trajectory analysis produces each participant a posterior probability (from 0 to 1) of belonging to a specific trajectory group. Based on posterior probabilities, the participants were assigned to the trajectory group where they had the highest posterior probability. A mean average posterior probability of 0.70 was set as a cut-off point to indicate that the trajectory encompasses participants with similar risk factor patterns and discriminates those with a different pattern [221].

Study I

To utilize all the available repeatedly measured physical activity exposure data, the area under the curve (AUC) for continuous PAIs was evaluated to indicate a long-term exposure to physical activity [222]. The subject-specific curves for PAI was estimated using the mixed model regression splines [223]. The covariance structure for the longitudinal setting was modeled by allowing for subject-specific regression spline coefficients, which were incorporated as random effects into the model. To avoid overfitting, the number of knots was reduced (two knots on the calendar time from 1980 to 2011) for the subject-specific part from that of the fixed effect part (four knots on age from three to 34 years). The mean profile was allowed to vary

across birth cohorts and sex in terms of possibly different fixed effects parts. Similar to the approach of Lai et al. (2014) [222], the AUC was evaluated as a measure of a long-term accumulation of the PAIs. The AUC variable for PAI was defined separately for childhood (six to 12 years), adolescence (12 to 18 years), young adulthood (18 to 24 years), and early life (six to 24 years). For interpretability, the AUC variables were standardized, resulting in normally distributed variables with mean zero and SD one.

Due to the longer intervals between the adulthood follow-up studies, applying the AUC approach for the adulthood physical activity exposure would have required more estimation and negatively affected the reliability of the AUC variables for adulthood physical activity. Therefore, the AUC approach was not applied to calculate adulthood physical activity exposure. To evaluate physical activity exposure in adulthood (between ages 24 to 37 years), an average value of the PAI was calculated over the adulthood follow-up period (follow-up years: 2001–2011), during which each subject had one to three PAI assessments. Subjects with one adulthood PAI assessment (N = 695) were not excluded from the analyses, as physical activity has previously been reported to remain stable in adulthood [224]. For interpretability, the adulthood physical activity variable was standardized, resulting in normally distributed variable with mean 0 and SD 1.

Linear regression analyses were conducted to investigate the associations of childhood, adolescence, young adulthood, and adulthood physical activity with midlife cognitive performance. All the regression analyses were conducted as multivariable models using the standardized principal components for cognitive performance as outcome variables and adjusting first for sex, age, childhood SES, and physical activity exposure in adulthood for the age window between 6 and 24, as well as for physical activity exposure in childhood for adulthood (Model 1). Afterwards, all the analyses were further adjusted for childhood school performance, education, systolic blood pressure, serum total cholesterol, and BMI at the time of cognitive testing (Model 2). The possible effect modification of age and sex for the studied associations were analyzed by adding the interaction terms (sex * physical activity, age * physical activity) into the fully adjusted models (Model 2).

Study II

In systolic and diastolic blood pressure, serum lipids, and BMI trajectory analyses participants who used antihypertensive (N = 273) or dyslipidemia medication (N = 100) in adulthood follow-ups were excluded from the risk factor-specific trajectory modeling analyses. The serum triglyceride measurements above 10 mmol/l were excluded from the triglyceride trajectory modeling analyses. The BMI measurements obtained during participants' pregnancies were excluded from the BMI trajectory

modeling analyses. All other participants were included in trajectory analyses but, for reliability, minimum of three measurements were required with at least one being from childhood and adolescence (nine to 18 years of age) and at least one from adulthood (21 to 49 years of age). None of the risk factors were normally distributed within the age group, and therefore the risk factors were first normalized using rank order normalization procedure within the age groups resulting in normally distributed components each with mean zero and SD one. At the first step in trajectory modeling, the number of trajectories was decided by using quadratic model. The choice of the number of trajectory groups were based on goodness of fit (2*ΔBIC), proportion of subjects classified in each group with a posterior probability >0.70, and values of mean posterior class membership probabilities as well as clinical plausibility. For meaningful statistical analyses linking risk factor trajectories and cognitive performance, frequency of >5% was preferred for the trajectory groups (not applicable for BMI due to clinical and statistical aspects). Finally, the shape of each trajectory group was decided by comparing goodness of fit (2*ΔBIC) between quadratic and cubic order term. These steps resulted in seven individual trajectory models for systolic and diastolic blood pressure, serum lipids, and BMI (Figures 2 to 8) with adequate fit to data, good classification accuracy and a strong clinical interpretability. Sex-specific trajectory modeling was performed for each risk factor (Figures 2 to 8), and the results were similar to the analyses for all participants. Therefore, to increase the statistical power the analyses for cognitive performance were conducted among all participants.

Linear regression analyses were conducted to investigate the associations for cardiovascular risk factor trajectory groups and midlife cognitive performance. All regression analyses were conducted as multivariable models using the standardized principal components for cognitive performance as outcome variables and adjusting for age, sex, and polygenic risk score. Furthermore, fully adjusted model included additionally other adulthood cardiovascular risk factors (systolic blood pressure, serum total cholesterol, BMI, serum fasting glucose, smoking, physical activity, and diet). Additionally, all analyses were further adjusted for childhood school performance, childhood SES, and education.

The analyses for cardiovascular risk factor trajectories were adjusted for other adulthood risk factors, and therefore, a mean value of the measurements in adulthood follow-up studies (follow-up years 2001, 2007, and 2011) was calculated for PAI indices, diet scores and other cardiovascular risk factor covariates (systolic blood pressure, serum total cholesterol, BMI, and serum fasting glucose) to indicate longitudinal exposure.

Study III

In the Young Finns Study, the serum creatinine levels were measured only in the adulthood follow-up studies. To ensure that only those participants with clinically normal serum creatinine were included in the trajectory modeling, those with self-reported (N = 12) and register-based diagnosis (N = 12) of kidney disease, and those with eGFR <60ml/min/1.73m^2 in any of the follow-up studies (N = 6) were excluded (total N = 30). Furthermore, the single serum creatinine measurements obtained after kidney injury (N = 4) or during the participants' pregnancy [175] (N = 74) were excluded from the trajectory modeling analyses. Finally, all the participants with at least two of the three serum creatinine measurements were included in the trajectory analyses. The number and shape of the trajectory groups were decided based on clinical plausibility and standard criteria: the BIC, indicating the goodness of fit of the models, and posterior probability, indicating internal the reliability of each participant belonging to a specific trajectory group. The participants were assigned to the trajectory group where they had the highest posterior probability to belong. For meaningful statistical analyses linking serum creatinine trajectories and cognitive performance, a frequency of >5% was preferred for the trajectory groups. Lastly, the individual trajectory models for serum creatinine in men and women were formed (Figure 9) with adequate fit to data, good classification accuracy, and a strong clinical interpretability.

The analysis of variance or the Kruskal-Wallis test was used for continuous variables, and the Cochran-Mantel-Haenszel test for categorical variables to investigate the risk factor levels between the trajectory groups. Linear regression analyses were conducted to investigate the associations between sex-stratified serum creatinine groups and midlife cognitive performance. All the regression analyses were conducted as multivariable models using the standardized principal components for cognitive performance as outcome variables. The analyses between serum creatinine groups and midlife cognitive performance were first adjusted for age, childhood school performance, and education (Model 1). Subsequently, the analyses were further adjusted for APOE, systolic blood pressure, serum total cholesterol, BMI, smoking, physical activity, diet, antihypertensive medication, and diabetes and impaired fasting glucose (Model 2). The possible effect modification of age as well as those risk factors known to associate with glomerular hyperfiltration or serum creatinine (systolic blood pressure, BMI, smoking, physical activity, diet, antihypertensive medication, diabetes and impaired fasting glucose, Homeostatic Model Assessment of Insulin Resistance, and HbA1c) for the studied associations were analyzed by adding the multiplicative interaction terms (e.g., age * serum creatinine groups, systolic blood pressure * serum creatinine groups) into the fully adjusted models (Model 2).

5 Results

5.1 Characteristics of the study population (I–III)

Of the 3,596 Young Finns Study participants at baseline in 1980, 2,062 attended the clinical examination in 2011, out of which 2,026 attended the cognitive testing (1,104 women and 922 men; age 10.8 years at baseline and 41.8 years at cognitive testing). The characteristics of the study population who participated in the cognitive testing of the latest Young Finns Study 31-year follow-up study in 2011 are presented in Table 6.

In the 2011 follow-up study, men had a worse risk factor profile than women. Specifically, men had lower childhood school performance, fewer years of education in adulthood, more smoking in early life and adulthood, and more dyslipidemia medication use. Furthermore, men had adverse levels in systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, BMI, physical activity index, and diet score. Additionally, men had higher serum creatinine and higher eGFR levels.

In cognitive testing, the male sex was directly associated with short-term working memory (SWM test), reaction and movement time (RTI test), and visual processing and sustained attention (RVP test) compared to the female sex in the age- and education-adjusted analyses (Table 7). Furthermore, in the age and education-adjusted analyses, compared to male sex, a weak direct association between female sex and episodic memory and associative learning (PAL test) was observed (Table 7).

The representativeness of the study population participating in the cognitive testing was examined by comparing the study baseline (1980) data between the participants and non-participants (Table 8). The participants lost to the follow-up were more often men and younger and, therefore, further attrition analyses were adjusted for age and sex. The non-participants originated from families with lower income, had lower childhood school performance, and higher childhood diastolic blood pressure. No other differences were observed.

Table 6. Characteristics of the study population participating in cognitive testing in 2011.

Background characteristics	N	All	Women (N = 1,104)	Men (N = 922)	P value
Age	2,026				
At baseline		10.8 (5.0)	10.9 (5.0)	10.7 (5.0)	0.421
At cognitive testing		41.8 (5.0)	41.9 (5.0)	41.7 (5.0)	0.421
Family income at baseline, n (%)	1,956				0.872
<17,000 euros/year		512 (26.2)	283 (26.6)	229 (25.7)	
17,000 – 27,000 euros/year		575 (29.4)	305 (28.6)	270 (30.3)	
27,000 – 37,000 euros/year		425 (21.7)	234 (22.0)	191 (21.5)	
>37,000 euros/year		444 (22.7)	244 (22.9)	200 (22.5)	
Childhood school performance, grade point average	1,777	7.77 (0.72)	7.94 (0.68)	7.56 (0.71)	<0.0001
Years of education in adulthood	1,928	14.9 (2.8)	15.2 (2.7)	14.6 (2.8)	<0.0001
Smoking earlier in life, n (%), yes	1,968	544 (27.6)	253 (23.5)	291 (32.6)	<0.0001
Smoking in adulthood, n (%), yes	2,017	494 (24.5)	233 (21.1)	261 (28.6)	0.0001
Adulthood antihypertensive medication use, n (%), yes	2,018	221 (11.0)	122 (11.1)	99 (10.8)	0.863
Adulthood dyslipidemia medication use, n (%), yes	2,018	87 (4.3)	29 (2.6)	58 (6.3)	<0.0001
Apolipoprotein E ε4 carriers, N (%) yes	1,909	680 (35.6)	366 (34.8)	314 (36.6)	0.421
Cardiovascular risk factors at the time of cognitive testing					
Systolic blood pressure, mmHg	2,019	118.9 (14.1)	115.6 (13.8)	122.9 (13.3)	<0.0001
Diastolic blood pressure, mmHg	2,019	74.9 (10.5)	72.4 (9.5)	77.8 (10.8)	<0.0001
Total cholesterol, mmol/l	2,008	5.18 (0.95)	5.07 (0.88)	5.32 (1.01)	<0.0001
LDL cholesterol, mmol/l	1,961	3.27 (0.83)	3.14 (0.75)	3.43 (0.89)	<0.0001
HDL cholesterol, mmol/l	2,006	1.33 (0.33)	1.43 (0.33)	1.20 (0.30)	<0.0001
Triglycerides, mmol/l	2,008	1.34 (1.23)	1.13 (1.21)	1.58 (1.21)	<0.0001
Body mass index, kg/m^2	2,020	26.53 (5.07)	26.14 (5.53)	27.00 (4.42)	<0.0001
Physical activity index	1,852	9.0 (1.9)	9.1 (1.9)	8.9 (1.9)	0.012
Diet score	1,429	2.1 (0.9)	2.3 (0.9)	1.9 (0.8)	<0.0001
Serum creatinine, µmol/l	1,996	76.95 (12.78)	70.20 (9.04)	84.92 (11.93)	<0.0001
Estimated GFR, ml/min/1.73 m^2	1,996	94.81 (12.45)	92.90 (12.75)	97.07 (11.71)	<0.0001

Values are means (SD) for the continuous variables and numbers (percentages) for categorical variables. The student's t-test or the Wilcoxon rank sum test was applied for analyses for continuous variables. Associations between categorical variables were studied with the χ^2 test. Socioeconomic status in childhood was defined as in four different strata that were dependent on an annual income of the family at baseline in 1980. Childhood school performance was defined as grade point average (range 4–10), i.e., mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline. Years of education was determined as a continuous variable from self-reported data on total years of education attained in adulthood until the year 2011. Early life smoking status was dichotomized into daily smokers (daily smoking in any of the early life follow-up time points between 12 and 24 years

of age) and nonsmokers. Adulthood smoking status was dichotomized into daily smokers (daily smoking in any of the adulthood follow-up studies 2001, 2007, or 2011) and nonsmokers. The participants reporting use of antihypertensive or dyslipidemia medication in any adulthood follow-up studies were defined as those with antihypertensive dyslipidemia medication use. APOE ε4 carriers were the participants with either one or two ε4 alleles, while the non-carriers were those without any ε4 allele. Physical activity was assessed with a standardized questionnaire and a physical activity index was calculated (range 5–15). The diet score in adulthood was based on intake levels of ideal five dietary metrics (range 0–5): fruits and vegetables, fish, whole grains, sodium, and sugar-sweetened beverages. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) serum creatinine-based equation. LDL = low-density lipoprotein. HDL = high-density lipoprotein.

Table 7. Cognitive components.

	Women (N = 1,104)	**Men (N = 922)**	**N, model**	**P value**
Paired Associates Learning test	0.05 (0.99)	-0.06 (1.01)	1,756	0.067
Spatial Working Memory test	-0.16 (0.96)	0.20 (1.01)	1,914	<0.0001
Reaction Time test	-0.18 (0.94)	0.22 (1.03)	1,731	<0.0001
Rapid Visual Information Processing test	-0.06 (0.97)	0.07 (1.03)	1,879	<0.0001

Values are means (SD) for continuous variables and n (%) for categorical variables. Cognitive components were standardized; mean = 0, SD = 1. P values are from linear regression models which were adjusted for age and education. A principal component analysis was used to calculate components indicating episodic memory and associative learning (Paired Associates Learning test), short-term working memory (Spatial Working Memory test), reaction and movement time (Reaction Time test), and visual processing and sustained attention (Rapid Visual Information Processing test) in the Cambridge Neuropsychological Test Automated Battery (CANTAB®).

Table 8. Comparison of the cognitive testing between the participants and the non-participants.

	N	Participants (N = 2,026)	Non-participants (N = 1,570)	P value
Sex	3,596			<0.0001
Women	1,832	1,104 (54.5)	728 (46.4)	
Men	1,764	922 (45.5)	842 (53.6)	
Age at baseline (1980)	3,596	10.8 (5.0)	9.9 (4.9)	<0.0001
Family income at baseline, n (%)	3,453			0.0004
<17,000 euros/year	950	512 (26.2)	438 (29.3)	
17,000–27,000 euros/year	1,054	575 (29.4)	479 (32.0)	
27,000–37,000 euros/year	734	425 (21.7)	309 (20.6)	
>37,000 euros/year	715	444 (22.7)	271 (18.1)	
Childhood school performance, grade point average	3,070	7.77 (0.73)	7.65 (0.74)	0.0001
Years of education in adulthood (follow-up year 2001)	2,604	14.7 (3.1)	14.0 (3.1)	0.883
Smoking earlier in life, n (%), yes	3,379	544 (27.6)	397 (28.1)	0.837
Apolipoprotein E ε4 carriers, N (%) yes	2,643	680 (35.6)	273 (37.2)	0.485
Cardiovascular risk factors at baseline (in 1980)				
Systolic blood pressure, mmHg	3,549	112.8 (11.9)	112.2 (12.5)	0.271
Diastolic blood pressure, mmHg	3,000	68.6 (9.4)	69.0 (9.8)	0.050
Total cholesterol, mmol/l	3,554	5.29 (0.90)	5.31 (0.93)	0.761
LDL cholesterol, mmol/l	3,551	3.42 (0.82)	3.45 (0.86)	0.756
HDL cholesterol, mmol/l	3,551	1.56 (0.31)	1.56 (0.31)	0.769
Triglycerides, mmol/l	3,554	0.67 (0.31)	0.66 (0.32)	0.343
Body mass index, kg/m^2	3,567	18.0 (3.1)	17.7 (3.1)	0.187
Physical activity index	2,351	9.0 (1.8)	9.1 (1.8)	0.263

Values are means (SD) for the continuous variables and numbers (%) for categorical variables. The Wilcoxon rank sum test and the χ^2-test were used to study the differences between the participants and the non-participants in age and sex. Due to significant differences in age and sex all the other analyses were adjusted for age and sex. Linear regression models were used for continuous variables and logistic regression for binary variables. Serum triglyceride values were log-transformed before analyses due to skewed distributions. Socioeconomic status in childhood was defined in four different strata that were dependent on an annual income of the family. Childhood school performance was defined as grade point average (i.e., mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline). Years of education was determined as a continuous variable from the self-reported data concerning total years of education attained in adulthood until the year 2001. Subjects who reported current smoking at any of the follow-up phases at the ages between 12 and 24 were classified as early life smokers. APOE ε4 carriers were the participants with either one or two ε4 alleles, while the non-carriers were those without any ε4 allele. LDL = low-density lipoprotein. HDL = high-density lipoprotein. Physical activity was assessed with a standardized questionnaire and a physical activity index was calculated (range 5–15).

5.2 Physical activity (I)

5.2.1 Physical activity accumulation from childhood to adulthood and cognitive performance

Physical activity accumulation in childhood, adolescence, and young adulthood was associated with faster reaction and movement time (RTI test) in the age, sex, childhood SES, and adulthood physical activity-adjusted analyses (Model 1, Table 9). Similarly, physical activity in adulthood was associated with faster reaction and movement time and, additionally, better visual processing and sustained attention in the age, sex, childhood SES, and childhood (age six to 12 years) physical activity-adjusted analyses (Model 1). After adding childhood school performance, education, systolic blood pressure, serum total cholesterol, and BMI into the multivariable model (Model 2), the associations of physical activity remained essentially similar for reaction and movement time but diluted for visual processing and sustained attention (Table 9).

5.2.2 Effect modification of age and sex

The possible effect modification of age and sex on physical activity accumulation in early life (age six to 24 years) and adulthood (age 24 to 37 years) on cognitive performance was studied by introducing multiplicative interaction terms for each possible modifier (physical activity * sex and physical activity * age at the time of cognitive testing) separately into the fully adjusted linear regression models (Model 2). No significant interactions with age were found.

For short-term working memory (SWM test), a significant interaction was found between sex and adulthood physical activity ($p = 0.015$). In addition, a weak interaction between sex and early life physical activity was found for short-term working memory ($p = 0.091$). For visual processing and sustained attention, a significant interaction was found between sex and early life physical activity ($p = 0.043$), while the interaction of adulthood physical activity was nonsignificant ($p = 0.118$). Due to the modifying effect of sex on associations between physical activity, short-term working memory, and visual processing and sustained attention, the analyses of these cognitive domains were conducted separately for women and men in all the studied physical activity age windows.

In men, physical activity accumulation in adulthood was directly associated with short-term working memory in the age, childhood SES, and childhood physical activity-adjusted analyses (Model 1, Table 10). After adding childhood school performance, education, systolic blood pressure, serum total cholesterol, and BMI into the multivariable model (Model 2), the association remained essentially similar, but the statistical significance was diluted. No associations were found between the physical activity of women in any of the studied age windows and short-term working memory.

In men, physical activity accumulation in young adulthood and adulthood was directly associated with visual processing and sustained attention in the age, childhood SES, childhood physical activity-adjusted analyses (Model 1, Table 10). Additionally, a weak direct association was found for adolescent physical activity on visual processing and sustained attention. After adding childhood school performance, education, systolic blood pressure, serum total cholesterol, and BMI into the multivariable model (Model 2), all the associations were diluted. The covariate mainly responsible for the dilution of the effect of physical activity was childhood school performance. No associations were found between the physical activity of women in any of the studied age windows and visual processing and sustained attention.

Table 9. Associations between cumulative exposure to physical activity (PA) and cognitive performance.

	Model 1		**Model 2**	
	β estimate (95% CI)	**P value**	**β estimate (95% CI)**	**P value**
Episodic memory and associative learning (PAL test; N = 1,359)				
PA in childhood (6–12 years)	-0.029 (-0.092–0.034)	0.373	-0.034 (-0.096–0.028)	0.282
PA in adolescence (12–18 years)	-0.006 (-0.068–0.056)	0.851	-0.024 (-0.085–0.037)	0.442
PA in young adulthood (18–24 years)	0.022 (-0.050–0.094)	0.550	-0.010 (-0.081–0.061)	0.781
PA in adulthood (24–37 years)	0.021 (-0.011–0.054)	0.191	0.005 (-0.027–0.037)	0.757
Short-term working memory (SWM test; N = 1,483)				
PA in childhood (6–12 years)	-0.031 (-0.091–0.029)	0.316	-0.036 (-0.095–0.024)	0.267
PA in adolescence (12–18 years)	-0.039 (-0.098–0.020)	0.200	-0.053 (-0.111–0.006)	0.079
PA in young adulthood (18–24 years)	-0.014 (-0.082–0.054)	0.678	-0.038 (-0.106–0.029)	0.516
PA in adulthood (24–37 years)	0.012 (-0.018–0.042)	0.424	0.004 (-0.027–0.034)	0.809
Reaction and movement time (RTI test; N = 1,338)				
PA in childhood (6–12 years)	0.119 (0.055–0.182)	0.0002	0.116 (0.053–0.179)	0.0003
PA in adolescence (12–18 years)	0.125 (0.063–0.188)	<0.0001	0.120 (0.057–0.182)	0.0002
PA in young adulthood (18–24 years)	0.135 (0.063–0.207)	0.0002	0.127 (0.055–0.199)	0.001
PA in adulthood (24–37 years)	0.045 (0.013–0.077)	0.006	0.036 (0.004–0.069)	0.028
Visual processing and sustained attention (RVP test; N = 1,454)				
PA in childhood (6–12 years)	0.009 (-0.052–0.070)	0.767	0.009 (-0.049–0.067)	0.769
PA in adolescence (12–18 years)	0.033 (-0.028–0.067)	0.291	0.013 (-0.045–0.070)	0.666
PA in young adulthood (18–24 years)	0.056 (-0.013–0.126)	0.111	0.017 (-0.050–0.083)	0.623
PA in adulthood (24–37 years)	0.041 (0.010–0.072)	0.010	0.013 (-0.017–0.043)	0.390

Values are β estimates and 95% confidence intervals (CIs) from linear regression models. Model 1 was adjusted with sex, age, childhood SES at baseline, and PA exposure in adulthood for age window between the ages 6 and 24, as well as for PA exposure in childhood for adulthood. Model 2 was further adjusted with childhood school performance, education, systolic blood pressure, serum total cholesterol, and BMI. The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Reproduced from the original publication I in the Medicine and Science in Sports and Exercise with permission of Wolters Kluwer Health, Inc.

Table 10. Associations between cumulative exposure to physical activity (PA), short-term working memory (SWM test) and visual processing and sustained attention (RVP test) separately among women (A) and men (B).

	Model 1 β estimate (95% CI)	P value	Model 2 β estimate (95% CI)	P value
A. Women				
Short-term working memory (SWM test; N = 836)				
PA in childhood (6–12 years)	-0.037 (-0.122–0.047)	0.387	-0.041 (-0.125–0.043)	0.338
PA in adolescence (12–18 years)	-0.047 (-0.132–0.038)	0.281	-0.065 (-0.149–0.019)	0.131
PA in young adulthood (18–24 years)	-0.008 (-0.104–0.089)	0.875	-0.042 (-0.138–0.055)	0.396
PA in adulthood (24–37 years)	-0.023 (-0.064–0.019)	0.288	-0.028 (-0.070–0.014)	0.187
Visual processing and sustained attention (RVP test; N = 818)				
PA in childhood (6–12 years)	-0.022 (-0.107–0.064)	0.621	-0.027 (-0.109–0.055)	0.516
PA in adolescence (12–18 years)	-0.025 (-0.112–0.061)	0.561	-0.052 (-0.135–0.030)	0.211
PA in young adulthood (18–24 years)	-0.003 (-0.100–0.095)	0.958	-0.055 (-0.149–0.039)	0.247
PA in adulthood (24–37 years)	0.016 (-0.026–0.057)	0.456	-0.005 (-0.046–0.036)	0.817
B. Men				
Short-term working memory (SWM test; N = 647)				
PA in childhood (6–12 years)	-0.021 (-0.106–0.064)	0.629	-0.032 (-0.117–0.054)	0.468
PA in adolescence (12–18 years)	-0.032 (-0.116–0.051)	0.447	-0.045 (-0.128–0.039)	0.293
PA in young adulthood (18–24 years)	-0.028 (-0.124–0.069)	0.577	-0.042 (-0.139–0.055)	0.393
PA in adulthood (24–37 years)	0.045 (0.001–0.089)	0.045	0.035 (-0.010–0.079)	0.126
Visual processing and sustained attention (RVP test; N = 636)				
PA in childhood (6–12 years)	0.033 (-0.056–0.121)	0.470	0.038 (-0.046–0.123)	0.372
PA in adolescence (12–18 years)	0.077 (-0.009–0.163)	0.081	0.066 (-0.016–0.148)	0.116
PA in young adulthood (18–24 years)	0.101 (0.001–0.200)	0.048	0.078 (-0.018–0.173)	0.111
PA in adulthood (24–37 years)	0.064 (0.018–0.110)	0.006	0.030 (-0.014–0.074)	0.182

Values are β estimates and 95% CIs from linear regression models. Model 1 was adjusted with age, childhood SES at baseline, and PA exposure in adulthood for age window between the ages 6 and 24, as well as for PA exposure in childhood for adulthood. Model 2 was further adjusted with childhood school performance, education, systolic blood pressure, serum total cholesterol, and BMI. The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Reproduced from the original publication I in the Medicine and Science in Sports and Exercise with permission of Wolters Kluwer Health, Inc.

5.3 Creation of the cardiovascular risk factor trajectories (II–III)

5.3.1 Systolic and diastolic blood pressure trajectories

After excluding participants using antihypertensive medication in 2001, 2007, or 2011 (N = 273) from the trajectory modeling analyses, N = 2,361 participants had at least three and 84.8% participants had at least four systolic blood pressure measurements (a median of five measurements), with at least one being from childhood and at least one from adulthood. In trajectory modeling, the indicator for better goodness of fit, 2*ΔBIC >10, was significant for the highest number of trajectory groups. Also, the posterior probabilities were above the 0.70 limit in every solution, but in addition, the group sizes were >5% for the five-group or less trajectory solutions. Therefore, the five-trajectory solution was considered the optimal number for the trajectory groups. After assessing the goodness of fit (2*ΔBIC >10) for the five-trajectory solution shapes, a final trajectory solution was chosen: (1) low-stable systolic blood pressure (N = 415, 17.6%) with consistently low systolic blood pressure level; (2) normal-stable systolic blood pressure (N = 935, 39.6%) with consistently normal (<120 mmHg) systolic blood pressure level; (3) moderate-stable systolic blood pressure (N = 399, 16.9%) with systolic blood pressure level consistently close to ideal (120 mmHg) [94]; (4) moderate-increasing systolic blood pressure (N = 471, 20.0%) with normal systolic blood pressure in childhood but continuously increasing blood pressure level from youth to midlife; (5) elevated-increasing systolic blood pressure (N = 141, 6.0%) individuals had elevated systolic blood pressure in childhood, and their blood pressure level increased throughout adulthood (Figure 2, Panel A). Sex-specific trajectory modeling was performed for systolic blood pressure, and the results were similar compared to the analyses of all the participants (Figure 2, Panels B and C).

After excluding participants using antihypertensive medication in 2001, 2007, or 2011 (N = 273) from the trajectory modeling analyses, N = 2,339 participants had at least three and 84.9% participants had at least four diastolic blood pressure measurements (a median of five measurements), with at least one being from childhood and at least one from adulthood. In trajectory modeling, the indicator for better goodness of fit, 2*ΔBIC >10, was significant for the highest number of trajectory groups. The posterior probabilities were above the 0.70 limit only for three or fewer trajectory solutions. Therefore, the three-group trajectory solution was considered optimal. After assessing the goodness of fit (2*ΔBIC >10) for the three-trajectory solution shapes, a final trajectory solution was chosen: (1) low-stable diastolic blood pressure (N = 326, 13.9%) with consistently low diastolic blood pressure level; (2) normal-stable diastolic blood pressure (N = 1,517, 64.9%) with

consistently close to ideal (<80 mmHg) diastolic blood pressure level [94]; (3) moderate-increasing diastolic blood pressure (N = 496, 21.2%) with normal diastolic blood pressure in childhood but continuously increasing diastolic blood pressure level from youth to midlife (Figure 3, Panel A). Sex-specific trajectory modeling was performed for diastolic blood pressure, and the results were similar compared to the analyses of all the participants (Figure 3, Panels B and C).

5.3.2 Serum lipid trajectories

After excluding the participants using dyslipidemia medication in 2001, 2007, or 2011 (N = 100) from the serum total cholesterol trajectory modeling analyses, N = 2,562 participants had at least three and 85.3% participants had at least four serum total cholesterol measurements (a median of five measurements), out of which at least one measurement was from childhood and at least one from adulthood. In trajectory modeling, the indicator for better goodness of fit, 2*ΔBIC >10, was significant for the highest number of trajectory groups. The posterior probabilities were above the 0.70 limit only for six or fewer trajectory solutions, but in addition, the group sizes were >5% for three-group or two-group trajectory solutions. Therefore, the three-group trajectory solution was considered the optimal number for trajectory groups. After assessing the goodness of fit (2*ΔBIC >10) for the three-group trajectory solution shapes, a final trajectory solution was chosen: (1) low-stable total cholesterol (N = 690, 26.9%) with consistently low serum total cholesterol; (2) elevated-stable total cholesterol (N = 1,409, 55.0%) with serum total cholesterol levels consistently close to ideal (<5.172 mmol/l) [94]; (3) high-stable total cholesterol (N = 463, 18.1%) with consistently high serum total cholesterol (Figure 4, Panel A). Sex-specific trajectory modeling was performed for serum total cholesterol, and the results were similar compared to the analyses of all the participants (Figure 4, Panels B and C).

After excluding participants using dyslipidemia medication in 2001, 2007, or 2011 (N = 100) from the serum LDL cholesterol trajectory modeling analyses, N = 2,541 participants had at least three and 84.8% participants had at least four serum LDL cholesterol measurements (a median of five measurements), out of which at least one measurement was from childhood and at least one from adulthood. In trajectory modeling, the indicator for better goodness of fit, 2*ΔBIC >10, was significant for the highest number of trajectory groups. The posterior probabilities were above the 0.70 limit for six or fewer trajectory solutions, but in addition, the group sizes were >5% for the three-group or two-group trajectory solutions. Therefore, the three-group trajectory solution was considered optimal. After assessing the goodness of fit (2*ΔBIC >10) for the three-trajectory solution shapes, a final trajectory solution was chosen: (1) low-stable LDL cholesterol (N = 977,

38.4%) with consistently low serum LDL cholesterol; (2) elevated-stable LDL cholesterol (N = 1,259, 49.6%) with serum LDL cholesterol levels consistently close to 3.5 mmol/l; (3) high-stable LDL cholesterol (N = 305, 12.0%) with consistently high serum LDL cholesterol (Figure 5, Panel A). Sex-specific trajectory modeling was performed for serum LDL cholesterol, and the results were similar compared to the analyses of all the participants (Figure 5, Panels B and C).

After excluding participants using dyslipidemia medication in 2001, 2007, or 2011 (N = 100) from the serum HDL cholesterol trajectory modeling analyses, N = 2,561 participants had at least three and 85.3% participants had at least four serum HDL cholesterol measurements (a median of five measurements), out of which at least one measurement was from childhood and at least one from adulthood. In trajectory modeling, the indicator for better goodness of fit, 2*ΔBIC >10, was significant for the highest number of trajectory groups. The posterior probabilities were above the 0.70 limit for seven or fewer trajectory solutions. The group sizes were >5% for five or less trajectory solutions. In addition, in the five-group trajectory solution, the average posterior probability in one group was 0.71, and in the four-group trajectory solutions, all the average posterior probabilities were above 0.84. Furthermore, the lowest minimum posterior probabilities were in the five-group trajectory solution only 0.35 in two groups, as in the four-group trajectory solution, all the minimum posterior probabilities were above 0.50. Therefore, because of lower average and minimum posterior probabilities as well as clinically less meaningful analyses linking HDL cholesterol and cognitive performance, the five-group trajectory solution was abandoned, and the four-group trajectory solution was considered optimal. After assessing the goodness of fit (2*ΔBIC >10) for the four-trajectory solution shapes, a final trajectory solution was chosen: (1) low-stable HDL cholesterol (N = 531, 20.7%) with consistently low serum HDL cholesterol; (2) normal-stable HDL cholesterol (N = 1,169, 45.7%) with serum HDL cholesterol levels consistently close to ideal (>1.2 mmol/l) [94]; (3) elevated-stable HDL cholesterol (N = 690, 26.9%) with consistently elevated serum HDL cholesterol; (4) high-stable HDL cholesterol (N = 171, 6.7%) with consistently high serum HDL cholesterol levels (close to 2 mmol/l) (Figure 6, Panel A). Sex-specific trajectory modeling was performed for serum HDL cholesterol, and the results were similar compared to the analyses of all the participants (Figure 6, Panels B and C).

After excluding participants using dyslipidemia medication in 2001, 2007, or 2011 (N = 100) and triglyceride measurements above 10 mmol/l from the serum triglyceride trajectory modeling analyses, N = 2,561 participants had at least three and 85.2% participants had at least four serum triglyceride measurements (a median of five measurements), out of which at least one measurement was from childhood and at least one from adulthood. In trajectory modeling, the indicator

for better goodness of fit, 2*ΔBIC >10, was significant for the highest number of trajectory groups. The posterior probabilities were above the 0.70 limit in all the trajectory solutions, but in addition, the group sizes were >5% for the three-group or two-group trajectory solutions. Therefore, the three-group trajectory solution was considered optimal. After assessing the goodness of fit (2*ΔBIC >10) for the three-trajectory solution shapes, a final trajectory solution was chosen: (1) low-stable triglycerides (N = 2,076, 81.1%) with consistently low serum triglycerides; (2) normal-increasing triglycerides (N = 349, 13.6%) with normal triglyceride levels in childhood but increasing triglyceride levels in midlife; (3) normal-rapidly increasing triglycerides (N = 136, 5.3%) with normal triglyceride levels in childhood but rapidly increasing triglyceride levels from youth to midlife (Figure 7, Panel A). Sex-specific trajectory modeling was performed for serum triglycerides, and the number of trajectory groups lowered in two in both women and men (Figure 7, Panels B and C).

5.3.3 BMI trajectories

In total, 2,588 participants had at least three and 83.8% participants had at least four BMI measurements (a median of five measurements), including at least one measurement from childhood and at least one from adulthood. The BMI measurements obtained during participants' pregnancies were excluded from the BMI trajectory modeling. In trajectory modeling, the indicator for better goodness of fit, 2*ΔBIC >10, was significant for the highest amount of trajectory groups. Also, the posterior probabilities were above the 0.70 limit in every solution, but the trajectory group size was already in the three-trajectory solution 6.14% for group three and in the four-trajectory solution 3.05% for group four. The three-trajectory solution was not considered clinically appropriate. The four-group trajectory solution was thus considered the optimal number for the trajectory groups. After assessing the goodness of fit (2*ΔBIC >10) for the 4-trajectory solution shapes, a final trajectory solution was chosen: (1) stable slim (N = 994, 38.4) with consistently low body weight; (2) stable normal weight (N = 1,104, 42.7%) with body weight consistently close to normal (25kg/m^2); (3) progressively overweight (N = 412, 15.9%), reached overweight in childhood/adolescence and gained weight throughout the adulthood; (4) persistently increasing obese (N = 78, 3.0%), reached obesity in childhood/adolescence and gained weight throughout adulthood (Figure 8, Panel A). Sex-specific trajectory modeling was performed for BMI, and the results were similar compared to the analyses of all the participants (Figure 8, Panels B and C).

5.3.4 Serum creatinine trajectories

In the Young Finns Study, the serum creatinine levels were measured only in the adulthood follow-up studies. The sex-stratified trajectory analyses were conducted because the serum creatinine concentration differs between women and men [163]. In men, 973 participants had at least two and 69.4% had the maximum of three serum creatinine measurements in adulthood. In trajectory modeling, the indicator for better goodness of fit, 2*ΔBIC >10, was significant for the highest amount of trajectory groups. Also, the posterior probabilities were above the 0.70 limit in every solution, but in addition, the group sizes were >5% for four-group or less trajectory solutions. Therefore, a trajectory solution with four groups was considered optimal (Figure 9): (1) 'high serum creatinine' (N = 71, 7.3%) with serum creatinine levels close to 100 μmol/l; (2) 'normal serum creatinine' (N = 295, 30.3%) with serum creatinine levels close to 90 μmol/l; (3) 'moderate serum creatinine' (N = 432, 44.4%) with serum creatinine levels close to 80 μmol/l; (4) 'low serum creatinine' (N = 175, 18.0%) with serum creatinine levels close to or over 70 μmol/l.

In women, 1,204 participants had at least two and 63.7% of these participants had the maximum of three serum creatinine measurements in adulthood. In trajectory modeling, the indicator for better goodness of fit, 2*ΔBIC >10, was significant for the five-group trajectory solution. The posterior probabilities were above the 0.70 limit for five or less trajectory solutions, but in addition, the group sizes were >5% for four or less trajectory solutions. Therefore, the trajectory solution including four groups was considered optimal (Figure 9): (1) 'high serum creatinine' (N = 146, 12.1%) with serum creatinine levels close to 80 μmol/l; (2) 'normal serum creatinine' (N = 360 29.9%) with serum creatinine levels close to 70 μmol/l; (3) 'moderate serum creatinine' (N = 558, 46.3%) with serum creatinine levels close to 65 μmol/l; (4) 'low serum creatinine' (N = 140, 11.6%) with serum creatinine levels below 55 μmol/l.

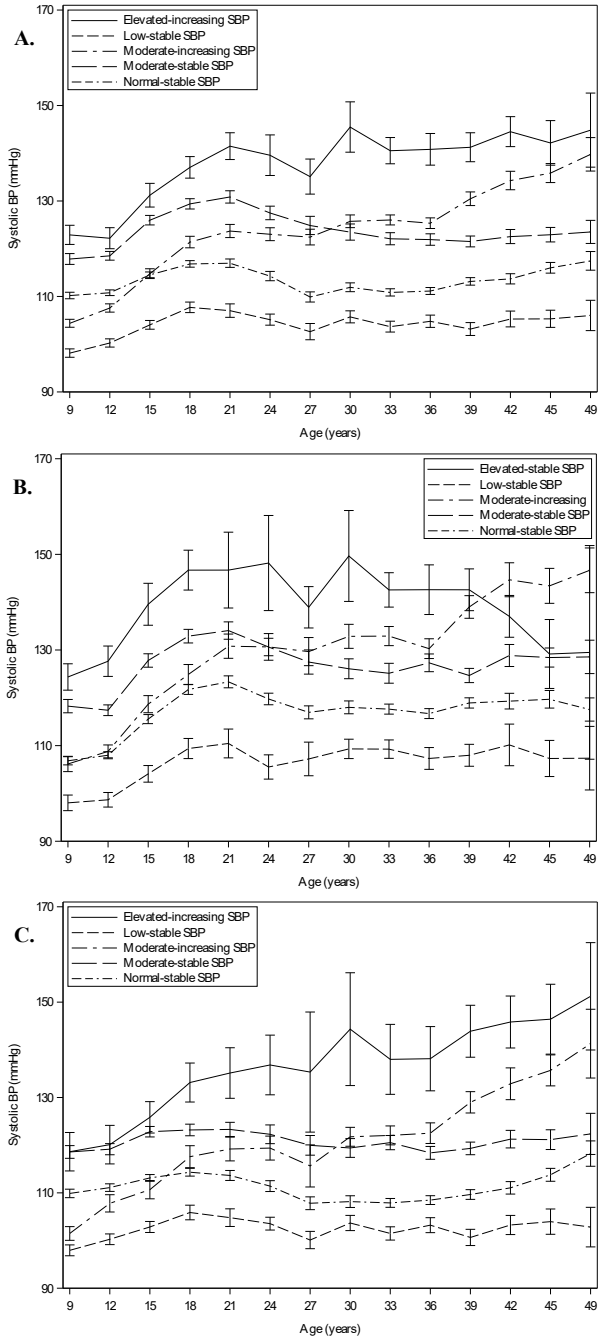

Figure 2. Trajectories from childhood to midlife for systolic blood pressure (SBP) for both sexes (A), and sex-specific trajectories for men (B) and women (C). Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

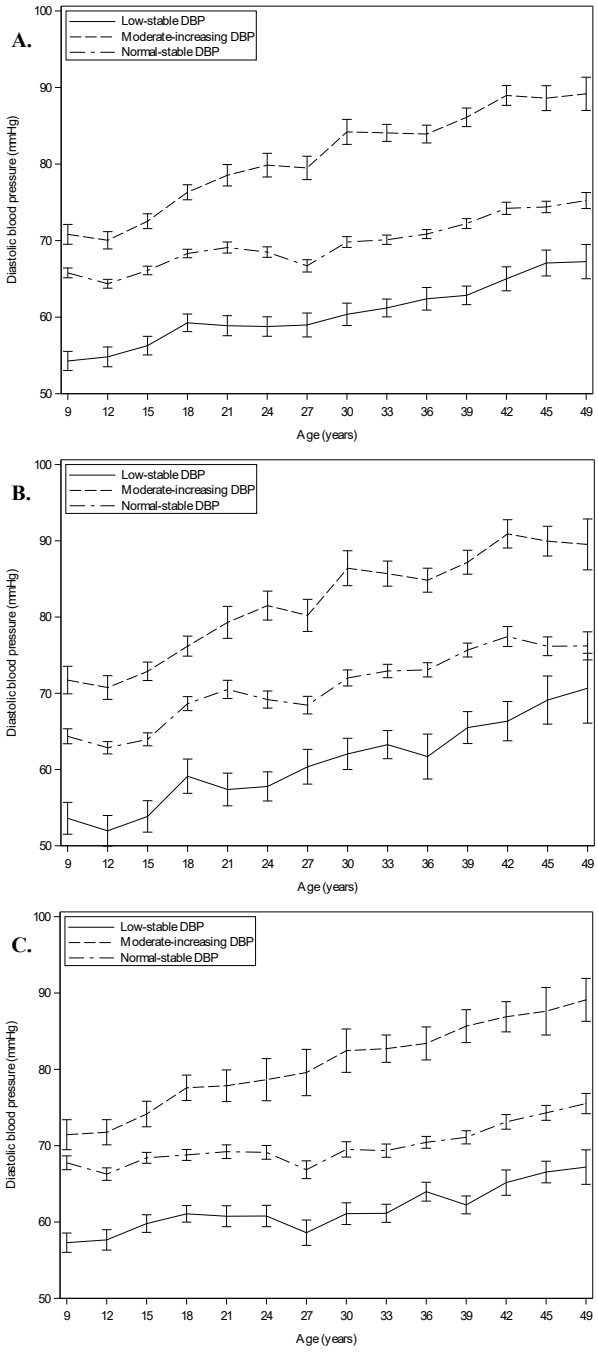

Figure 3. Trajectories from childhood to midlife for diastolic blood pressure (DBP) for both sexes (A), and sex-specific trajectories for men (B) and women (C). Reproduced from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

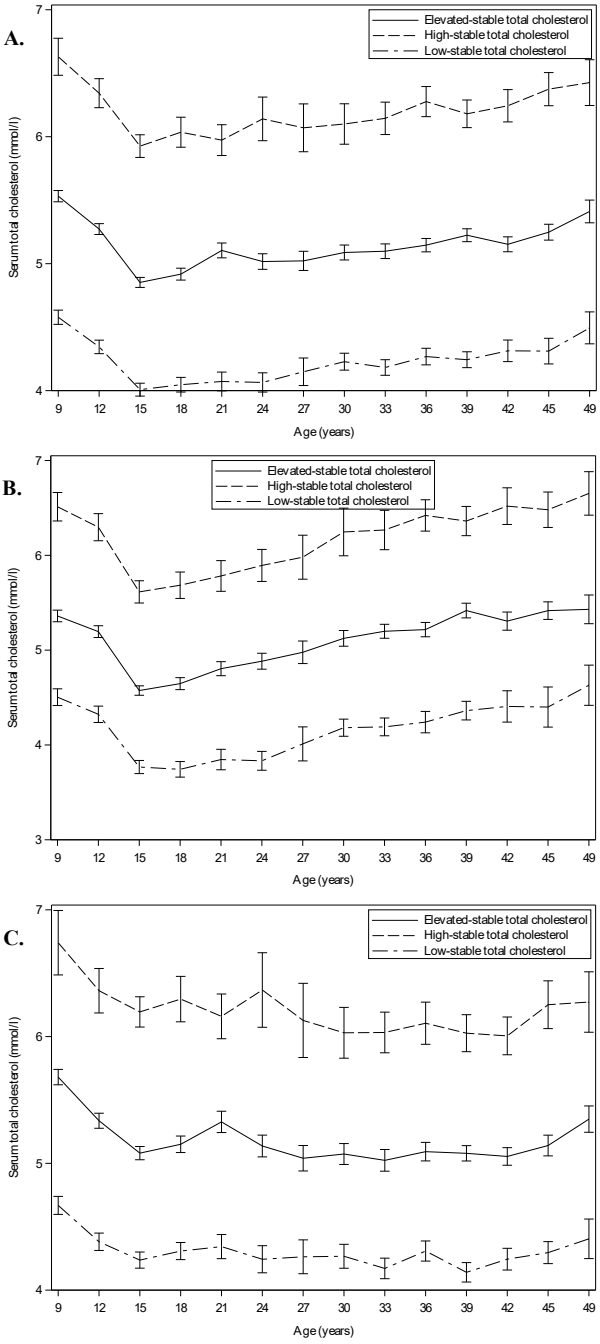

Figure 4. Trajectories from childhood to midlife for serum total cholesterol for both sexes (A), and sex-specific trajectories for men (B) and women (C). Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

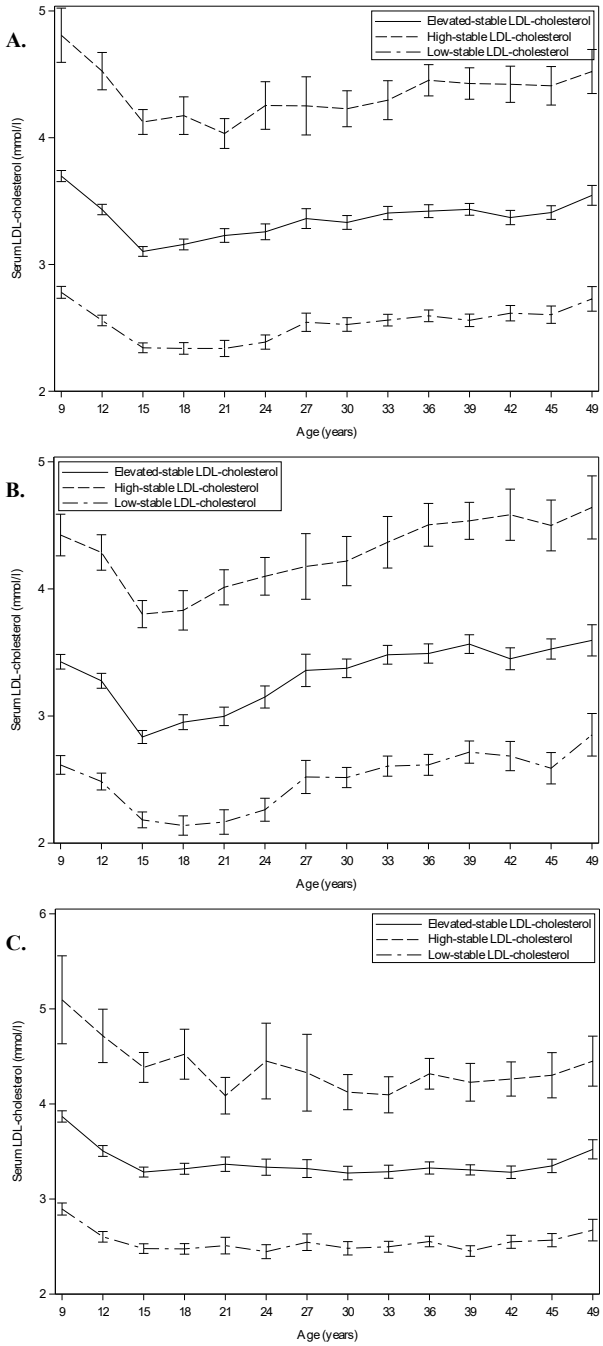

Figure 5. Trajectories from childhood to midlife for serum LDL cholesterol for both sexes (A), and sex-specific trajectories for men (B) and women (C). Reproduced from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

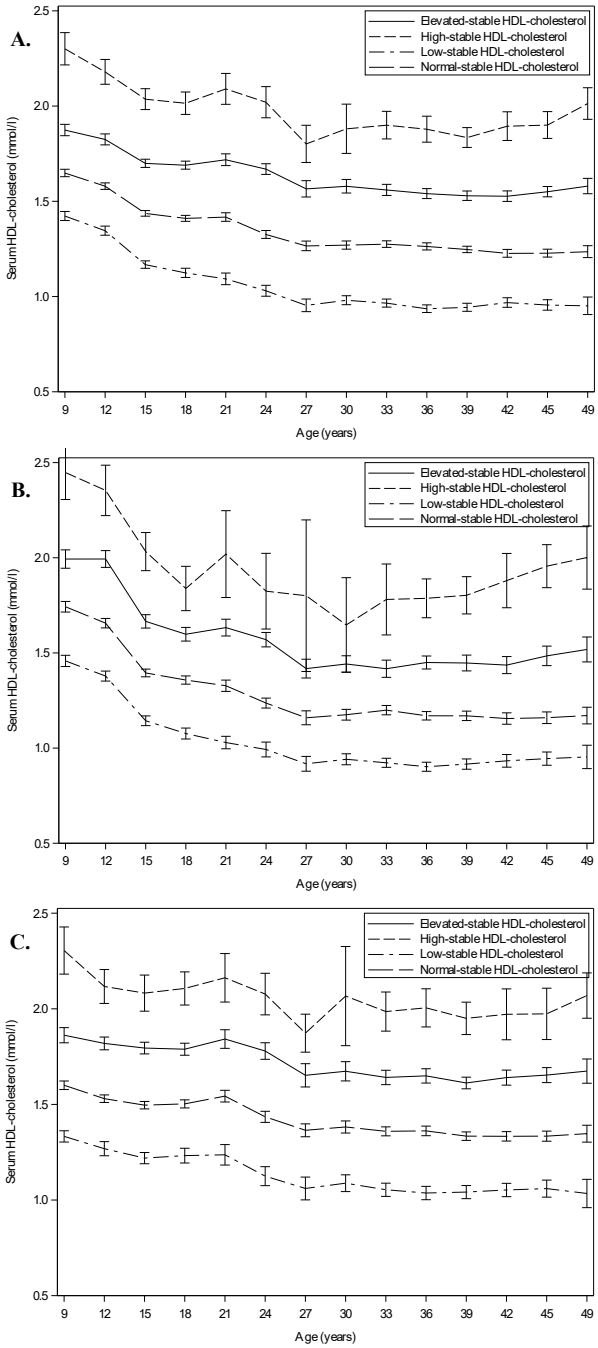

Figure 6. Trajectories from childhood to midlife for HDL cholesterol for both sexes (A), and sex-specific trajectories for men (B) and women (C). Reproduced from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

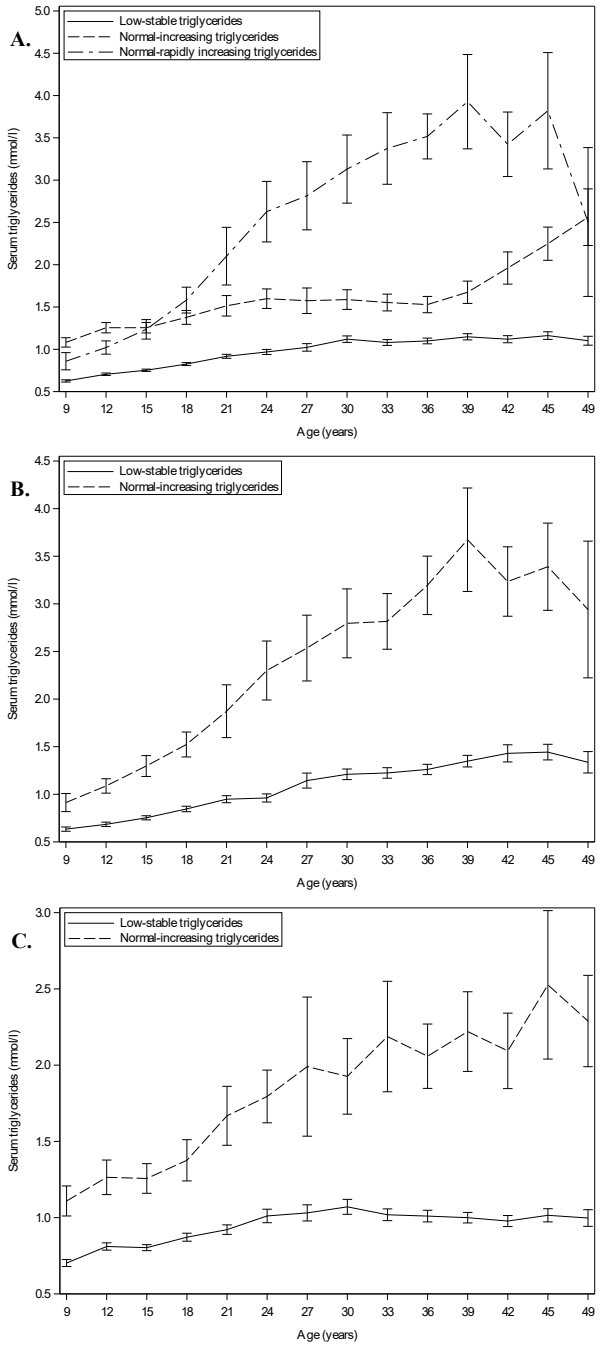

Figure 7. Trajectories from childhood to midlife for serum triglycerides for both sexes (A), and sex-specific trajectories for men (B) and women (C). Reproduced from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

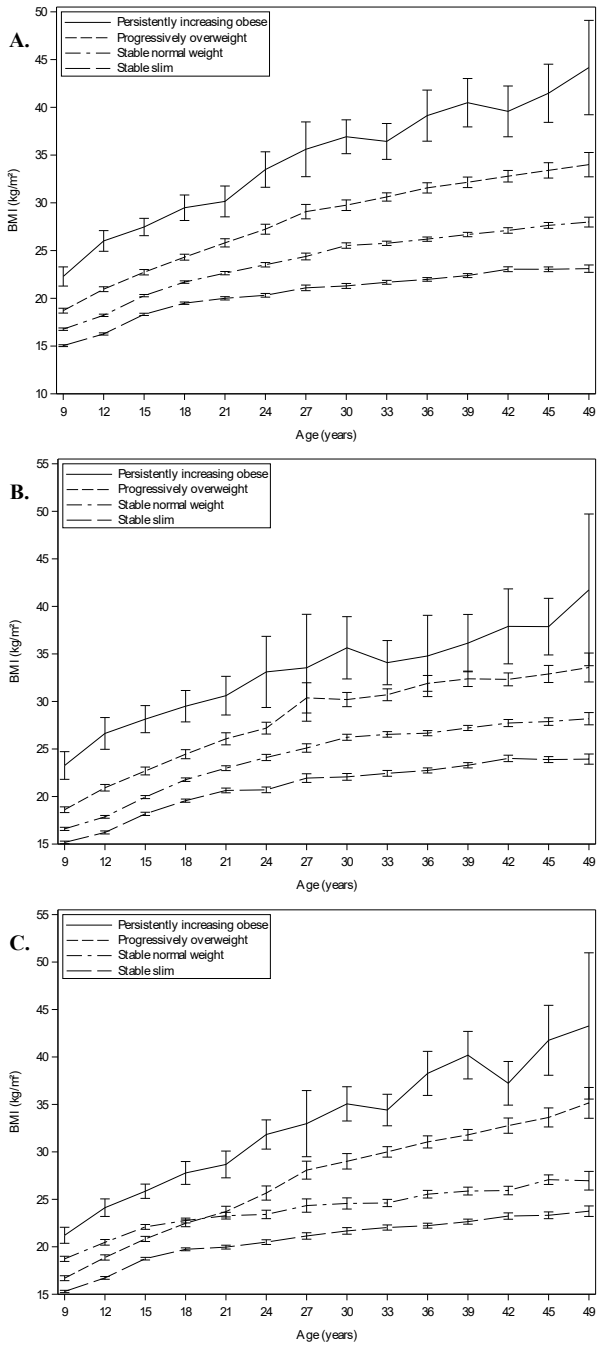

Figure 8. Trajectories from childhood to midlife for body mass index for both sexes (A), and sex-specific trajectories for men (B) and women (C). Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

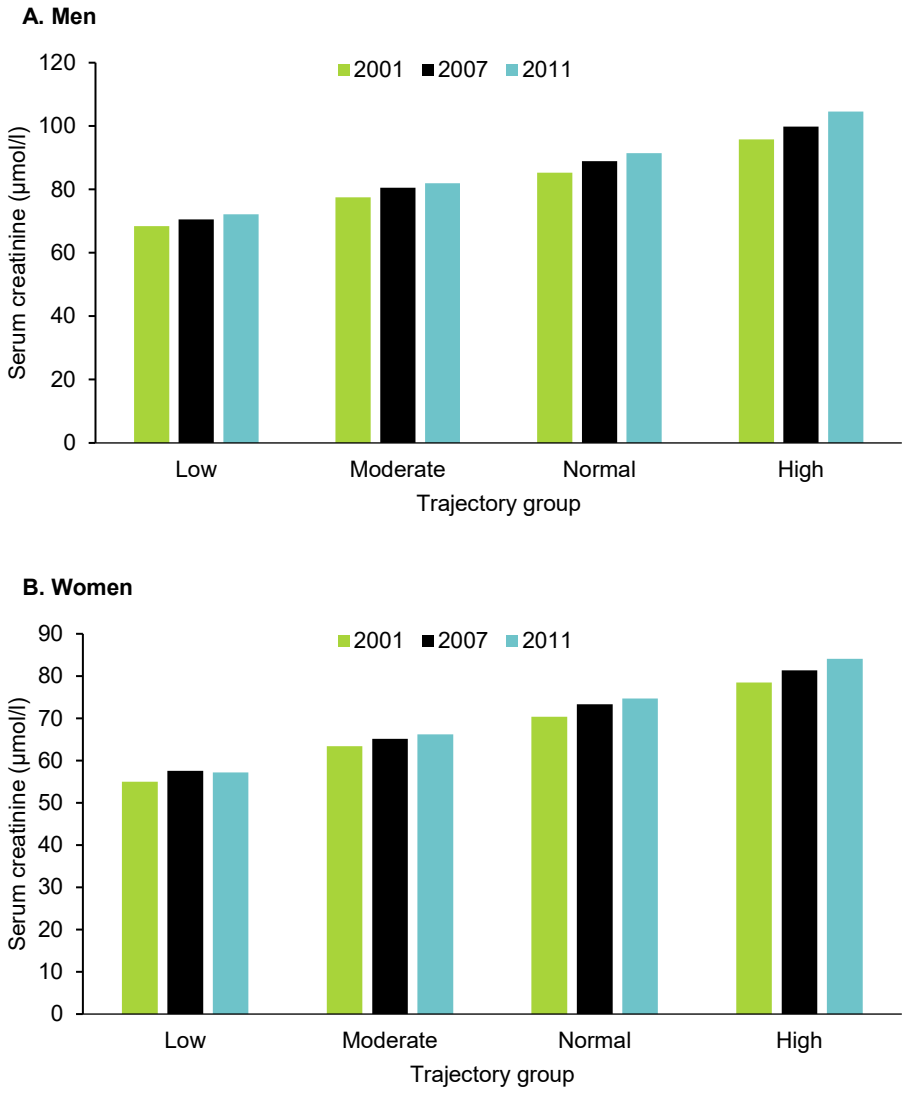

Figure 9. Trajectories from adulthood to midlife for serum creatinine for men (A) and women (B). Reproduced from the original publication III in the Neurology with permission of Wolters Kluwer Health, Inc.

5.4 Characteristics of cardiovascular risk factor trajectories (II)

The descriptive characteristics for each cardiovascular risk factor trajectory group are presented in Tables 11 and 12. For cardiovascular risk factor accumulation, a risk score was calculated using the adverse risk factor levels based on the cardiovascular risk factor trajectories (Table 13). To calculate the risk score, risk points were given to the participants belonging to 1) 'moderate-increasing systolic blood pressure' or 'elevated-increasing systolic blood pressure' groups, 2) 'high-stable total cholesterol' group, 3) 'progressively overweight' or 'persistently increasing obese' groups, and 4) those having antihypertensive or dyslipidemia medication in adulthood. Subsequently, the risk points were summed to form the risk score indicating the accumulation of longitudinal cardiovascular risk factors. The descriptive characteristics of the risk score groups are presented in Table 14. Among the participants with data on cognitive performance and polygenic risk score (N = 1,718), 826 of them did not have any risk factors, 598 had one of the three risk factors, 244 had two, and 50 had all three.

Table 11. Descriptive characteristics for the cardiovascular risk factor trajectory groups in blood pressure and BMI.

	N (%)		Systolic / diastolic blood pressure, mmHg (SD / SD)		Body mass index, kg/m^2 (SD)	
	Total *	Women **	In year 2001	In year 2011	In year 2001	In year 2011
A. Systolic blood pressure (N = 2,634)						
Normal-stable SBP	415 (15.8)	314 (75.7)	102.6 / 63.0 (7.5 / 8.2)	105.2 / 66.7 (7.5 / 8.2)	22.82 (3.41)	24.16 (3.90)
Low-stable SBP	935 (35.5)	621 (66.4)	110.4 / 67.0 (7.2 / 9.1)	113.4 / 71.6 (7.2 / 9.1)	24.36 (3.84)	25.70 (4.61)
Moderate-stable SBP	399 (15.0)	155 (38.8)	122.0 / 72.9 (7.8 / 8.1)	122.2 / 76.8 (7.8 / 8.1)	25.88 (4.04)	27.13 (4.62)
Moderate-increasing SBP	471 (17.9)	150 (31.8)	124.3 / 74.5 (7.9 / 11.3)	130.2 / 81.3 (7.9 / 11.3)	25.53 (3.98)	27.21 (4.76)
Elevated-increasing SBP	141 (5.4)	36 (25.5)	138.0 / 82.1 (11.3 / 12.7)	143.1 / 87.4 (11.3 / 12.7)	27.69 (4.82)	27.77 (4.27)
Antihypertensive medication ***	273 (10.4)	145 (53.1)	128.0 / 80.7 (14.3 / 14.7)	125.6 / 79.7 (14.3 / 14.7)	28.11 (5.82)	30.16 (6.56)
B. Diastolic blood pressure (N = 2,339)						
Low-stable DBP	326 (13.9)	204 (62.6)	107.6 / 59.5 (10.1 / 7.1)	109.3 / 64.4 (11.1 / 7.4)	23.0 (3.4)	24.5 (4.1)
Normal-stable DBP	1,517 (64.9)	871 (57.4)	113.1 / 68.0 (10.6 / 7.3)	116.4 / 72.8 (11.8 / 7.7)	24.5 (3.8)	25.8 (4.4)
Moderate-increasing DBP	496 (21.2)	191 (38.5)	126.7 / 81.5 (11.1 / 7.9)	131.2 / 86.9 (13.4 / 8.3)	26.6 (4.6)	28.2 (5.3)
C. Total cholesterol (N = 2,662)						
Low-stable total cholesterol	690 (25.9)	362 (52.5)	114.5 / 68.6 (12.6 / 13.0)	116.2 / 73.3 (12.6 / 13.0)	24.27 (3.96)	25.80 (4.81)
Elevated-stable total cholesterol	1,409 (52.9)	788 (55.9)	116.3 / 70.8 (12.9 / 14.0)	118.8 / 74.8 (12.9 / 14.0)	25.00 (4.45)	26.35 (4.88)
High-stable total cholesterol	463 (17.4)	253 (54.6)	120.0 / 73.4 (13.8 / 14.6)	123.0 / 77.1 (13.8 / 14.6)	25.96 (4.51)	27.14 (4.99)
Dyslipidemia medication ***	100 (3.8)	32 (32.0)	127.9 / 78.9 (15.4 / 13.5)	123.8 / 78.1 (15.4 / 13.5)	27.64 (4.80)	30.46 (6.57)
D. LDL cholesterol (N = 2,541)						
Low-stable LDL cholesterol	977 (38.5)	552 (56.5)	114.9 / 69.0 (12.7 / 10.2)	116.9 / 73.6 (13.2 / 10.1)	24.3 (4.1)	25.8 (4.8)
Elevated-stable LDL cholesterol	1,259 (49.6)	698 (55.4)	116.7 / 71.2 (12.8 / 10.5)	119.4 / 75.1 (14.2 / 10.3)	25.2 (4.5)	26.6 (4.9)
High-stable LDL cholesterol	305 (12.0)	151 (49.5)	117.7 / 71.6 (13.0 / 11.4)	122.2 / 76.8 (15.2 / 11.6)	26.0 (4.6)	27.1 (4.9)

	N (%)		Systolic / diastolic blood pressure, mmHg (SD / SD)		Body mass index, kg/m^2 (SD)	
	Total *	Women **	In year 2001	In year 2011	In year 2001	In year 2011
E. HDL cholesterol (N = 2,561)						
Low-stable HDL cholesterol	531 (20.7)	161 (30.3)	118.4 / 71.9 (13.6 / 11.9)	120.3 / 76.7 (13.6 / 10.8)	26.5 (4.6)	28.1 (4.9)
Normal-stable HDL cholesterol	1,169 (45.7)	631 (54.0)	116.0 / 70.4 (12.8 / 10.5)	118.9 / 74.8 (14.7/ 10.7)	25.0 (4.5)	26.5 (4.9)
Elevated-stable HDL cholesterol	690 (26.9)	484 (70.1)	115.4 / 70.1 (12.2 / 9.8)	117.8 / 73.5 (13.2 / 9.5)	24.0 (3.9)	25.3 (4.7)
High-stable HDL cholesterol	171 (6.7)	128 (74.9)	113.4 / 68.2 (11.8 / 9.9)	118.2 / 73.7 (14.9 / 10.1)	23.9 (3.3)	24.5 (4.0)
F. Triglycerides (N = 2,562)						
Low-stable triglycerides	2,076 (81.0)	1,162 (56.0)	115.2 / 69.7 (12.2 / 10.1)	118.1 / 71.8 (13.8 / 10.1)	24.6 (4.1)	26.0 (4.8)
Normal-increasing triglycerides	349 (13.6)	211 (60.5)	118.3 / 72.0 (14.2 / 11.6)	119.9 / 76.6 (15.0 / 11.0)	26.0 (5.0)	27.3 (4.8)
Normal-rapidly increasing	137 (5.4)	30 (21.9)	124.7 / 77.8 (14.1 / 12.2)	127.4 / 81.3 (13.6 / 10.3)	28.3 (4.1)	29.9 (4.8)
G. Body mass index (N = 2,588)						
Stable normal weight	994 (38.4)	611 (61.5)	113.4 / 68.3 (12.1 / 14.2)	116.2 / 72.3 (12.1 / 14.2)	21.62 (1.99)	22.64 (2.31)
Stable slim	1,104 (42.7)	530 (48.0)	116.8 / 71.1 (12.5 / 13.3)	119.3 / 75.5 (12.5 / 13.3)	25.61 (2.46)	27.01 (2.86)
Progressively overweight	412 (15.9)	214 (51.9)	121.8 / 74.7 (14.1 / 13.9)	124.3 / 79.3 (14.1 / 13.9)	30.06 (3.31)	32.64 (3.92)
Persistently increasing obese	78 (3.0)	41 (52.6)	128.6 / 79.2 (15.6 / 15.0)	126.7 / 78.3 (15.6 / 15.0)	37.52 (4.67)	39.70 (7.23)

Values are mean (SD) for continuous variables and numbers (%) for categorical variables. Year 2001 indicates follow-up year 21 and year 2011 indicates follow-up year 31. SBP = systolic blood pressure. DPB = diastolic blood pressure. LDL = low-density lipoprotein. HDL = high-density lipoprotein. *Percentages are calculated against the total population. **Percentages are calculated against the participants within each trajectory group. ***If participants had antihypertensive or dyslipidemia medication in any adulthood follow-up year 2001, 2007, or 2011, they were defined to belong to medication group and were excluded from the trajectory modeling. Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

Table 12. Descriptive characteristics for the cardiovascular risk factor trajectory groups in serum lipids.

	Total cholesterol, mmol/l (SD)		LDL cholesterol, mmol/l (SD)		HDL cholesterol, mmol/l (SD)		Triglycerides, mmol/l (SD)	
	In year 2001	In year 2011	In year 2001	In year 2011	In year 2001	In year 2011	In year 2001	In year 2011
A. Systolic blood pressure (N = 2,634)								
Normal-stable SBP	4.95 (0.92)	4.99 (0.95)	3.09 (0.80)	3.10 (0.76)	1.35 (0.32)	1.38 (0.35)	1.14 (0.55)	1.19 (2.00)
Low-stable SBP	5.07 (0.91)	5.13 (0.89)	3.22 (0.78)	3.23 (0.76)	1.32 (0.31)	1.37 (0.32)	1.19 (0.76)	1.16 (0.71)
Moderate-stable SBP	5.22 (0.92)	5.22 (1.00)	3.36 (0.83)	3.33 (0.90)	1.26 (0.33)	1.31 (0.35)	1.39 (0.82)	1.35 (1.29)
Moderate-increasing SBP	5.28 (1.05)	5.33 (0.99)	3.34 (0.88)	3.39 (0.88)	1.26 (0.31)	1.27 (0.32)	1.52 (1.05)	1.52 (1.07)
Elevated-increasing SBP	5.54 (0.98)	5.50 (0.95)	3.58 (0.83)	3.55 (0.86)	1.23 (0.31)	1.26 (0.32)	1.62 (0.96)	1.79 (1.60)
Antihypertensive medication *	5.43 (1.11)	5.20 (0.93)	3.50 (0.96)	3.25 (0.84)	1.21 (0.31)	1.23 (0.32)	1.65 (1.05)	1.66 (1.09)
B. Diastolic blood pressure (N = 2,339)								
Low-stable DBP	4.97 (0.89)	5.05 (0.93)	3.18 (0.79)	3.22 (0.79)	1.32 (0.31)	1.34 (0.32)	1.08 (0.48)	1.08 (0.66)
Normal-stable DBP	5.11 (0.95)	5.15 (0.96)	3.23 (0.82)	3.24 (0.82)	1.32 (0.31)	1.36 (0.33)	1.27 (0.83)	1.26 (1.38)
Moderate-increasing DBP	5.35 (0.99)	5.37 (0.93)	3.42 (0.83)	3.43 (0.84)	1.23 (0.33)	1.27 (0.33)	1.56 (0.96)	1.58 (1.11)
C. Total cholesterol (N = 2,662)								
Low-stable total cholesterol	4.23 (0.55)	4.29 (0.54)	2.54 (0.51)	2.56 (0.48)	1.22 (0.27)	1.26 (0.30)	1.05 (0.49)	1.06 (0.58)
Elevated-stable total cholesterol	5.17 (0.64)	5.23 (0.65)	3.29 (0.59)	3.32 (0.58)	1.29 (0.31)	1.34 (0.32)	1.33 (0.77)	1.31 (1.32)
High-stable total cholesterol	6.25 (0.81)	6.31 (0.84)	4.18 (0.83)	4.00 (0.96)	1.35 (0.36)	1.36 (0.38)	1.71 (1.21)	1.74 (1.49)
Dyslipidemia medication *	6.32 (1.30)	5.23 (1.22)	4.29 (1.18)	3.16 (1.10)	1.23 (0.31)	1.22 (0.34)	2.20 (2.00)	2.10 (2.26)
D. LDL cholesterol (N = 2,541)								
Low-stable LDL cholesterol	4.41 (0.61)	4.51 (0.67)	2.6 (0.49)	2.65 (0.49)	1.29 (0.30)	1.34 (0.34)	1.15 (0.65)	1.19 (1.41)
Elevated-stable LDL cholesterol	5.36 (0.71)	5.39 (0.70)	3.46 (0.56)	3.48 (0.56)	1.30 (0.32)	1.33 (0.32)	1.33 (0.69)	1.28 (0.80)
High-stable LDL cholesterol	6.30 (0.80)	6.45 (0.82)	4.38 (0.70)	4.51 (0.74)	1.26 (0.32)	1.30 (0.34)	1.47 (0.73)	1.57 (1.05)

	Total cholesterol, mmol/l (SD)		LDL cholesterol, mmol/l (SD)		HDL cholesterol, mmol/l (SD)		Triglycerides, mmol/l (SD)	
	In year 2001	In year 2011	In year 2001	In year 2011	In year 2001	In year 2011	In year 2001	In year 2011
E. HDL cholesterol (N = 2,561)								
Low-stable HDL cholesterol	5.05 (1.00)	5.11 (1.02)	3.33 (0.85)	3.34 (0.86)	0.94 (0.16)	0.97 (0.15)	1.73 (1.00)	1.89 (2.00)
Normal-stable HDL cholesterol	5.03 (0.93)	5.13 (0.95)	3.23 (0.82)	3.31 (0.82)	1.23 (0.20)	1.26 (0.20)	1.28 (0.71)	1.26 (0.78)
Elevated-stable HDL cholesterol	5.23 (0.88)	5.19 (0.83)	3.22 (0.75)	3.18 (0.76)	1.52 (0.22)	1.56 (0.22)	1.09 (0.52)	1.01 (0.50)
High-stable HDL cholesterol	5.46 (0.82)	5.63 (0.93)	3.15 (0.73)	3.28 (0.79)	1.83 (0.25)	1.93 (0.28)	1.06 (0.50)	0.91 (0.38)
F. Triglycerides (N = 2,562)								
Low-stable triglycerides	5.03 (0.89)	5.09 (0.89)	3.21 (0.78)	3.24 (0.79)	1.32 (0.30)	1.37 (0.32)	1.11 (0.47)	1.07 (0.49)
Normal-increasing triglycerides	5.38 (1.00)	5.43 (0.97)	3.40 (0.86)	3.43 (0.90)	1.23 (0.34)	1.24 (0.30)	1.66 (0.63)	1.71 (0.83)
Normal-rapidly increasing	5.83 (1.05)	5.91 (1.15)	3.47 (0.86)	3.46 (0.89)	0.97 (0.29)	0.96 (0.22)	3.25 (1.29)	3.83 (3.59)
G. Body mass index (N = 2,588)								
Stable normal weight	5.02 (0.93)	5.07 (0.94)	3.15 (0.80)	3.16 (0.78)	1.37 (0.30)	1.43 (0.33)	1.12 (0.60)	1.12 (1.39)
Stable slim	5.23 (1.01)	5.27 (0.95)	3.35 (0.86)	3.36 (0.85)	1.27 (0.32)	1.30 (0.32)	1.39 (0.93)	1.37 (0.88)
Progressively overweight	5.34 (0.98)	5.21 (0.95)	3.42 (0.84)	3.28 (0.82)	1.19 (0.31)	1.19 (0.30)	1.68 (1.06)	1.72 (1.49)
Persistently increasing obese	5.37 (1.01)	5.06 (0.98)	3.52 (0.92)	3.20 (0.92)	1.08 (0.23)	1.15 (0.23)	1.71 (0.78)	1.80 (1.78)

Values are mean (SD) for continuous variables. Year 2001 indicates follow-up year 21 and year 2011 indicates follow-up year 31. SBP = systolic blood pressure. DPB = diastolic blood pressure. LDL = low-density lipoprotein. HDL = high-density lipoprotein. *If participants had antihypertensive or dyslipidemia medication in any adulthood follow-up year 2001, 2007, or 2011, they were defined to belong to medication group and were excluded from the trajectory modeling. Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

Table 13. Creation of the cardiovascular risk factor score.

	Risk score points
Systolic blood pressure	
Low-stable SBP	0
Normal-stable SBP	0
Moderate-stable SBP	0
Moderate-increasing SBP	1
Elevated-increasing SBP	1
Antihypertensive medication *	1
Serum total cholesterol	
Low-stable total cholesterol	0
Elevated-stable total cholesterol	0
High-stable total cholesterol	1
Dyslipidemia medication *	1
Body mass index	
Stable slim	0
Stable normal weight	0
Progressively overweight	1
Persistently increasing obese	1
Total risk score, range	0–3

* If participant had antihypertensive or dyslipidemia medication in any adulthood follow-up year (2001, 2007 or 2011), they were defined to belong to medication group and were excluded from trajectory modeling. Reproduced from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

Table 14. Descriptive characteristics for cardiovascular risk factor score groups in follow-up year 2011.

Score	N (%) Total*	Women**	Systolic blood pressure, mmHg (SD)	Total cholesterol, mmol/l (SD)	Body mass index, kg/m^2 (SD)
0	826 (48.1)	523 (63.3)	112.2 (10.1)	4.89 (0.75)	24.36 (3.30)
1	598 (34.8)	303 (50.7)	122.9 (13.4)	5.29 (0.98)	27.01 (4.66)
2	244 (14.2)	98 (40.2)	129.7 (13.8)	5.64 (1.00)	30.68 (5.71)
3	50 (2.9)	17 (34.0)	134.4 (16.6)	5.66 (1.27)	34.98 (5.64)

Values are means (SD) for continuous variables and numbers (%) for categorical variables. Year 2011 indicates 31-year follow-up study. Risk points were given as described in the Table 13. The analyses were conducted among participants with data on cognitive performance and polygenic risk score for cognitive performance (N = 1,718). *Percentages are calculated against the total population. **Percentages are calculated against the participants within each trajectory group. Reproduced from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

5.5 Cardiovascular risk factor trajectories and cognitive performance (II)

Blood pressure and cognitive performance

Systolic blood pressure was found to be inversely associated with episodic memory and associative learning (PAL test). The 'elevated-increased systolic blood pressure' group had worse episodic memory and associative learning compared with the 'normal-stable systolic blood pressure' group (Table 15, Panel A) in age, sex, and polygenic risk score-adjusted analyses (Model 1). In addition, the 'moderate-increasing systolic blood pressure' group was inversely associated with visual processing and sustained attention (RVP test) compared with the 'normal-stable systolic blood pressure' group (Table 16, Panel A) in age, sex, and polygenic risk score-adjusted analyses (Model 1). After adding the adulthood cardiovascular risk factors (BMI, serum total cholesterol, fasting serum glucose, smoking, physical activity, and diet) to the multivariable model (Model 2), the associations for systolic blood pressure remained essentially similar (Table 15, Panel A, for episodic memory and associative learning, and Table 16, Panel A, for visual processing and sustained attention). Additionally, a better performance in the reaction and movement time (RTI test) was observed for the 'moderate-stable systolic blood pressure' group compared with the 'normal-stable systolic blood pressure' group (Table 17, Panel A). No associations were found between the systolic blood pressure trajectory groups and short-term working memory (SWM test, Table 18, Panel A). Additionally, no associations were found between the diastolic blood pressure trajectory groups and any of the cognitive domains (Tables 15 to 18).

Serum lipids and cognitive performance

An inverse association was found between serum total cholesterol and episodic memory and associative learning. The 'high-stable total cholesterol' group had worse episodic memory and associative learning compared with the 'low-stable total cholesterol' group (Table 15, Panel C) in age, sex, and polygenic risk score-adjusted analyses (Model 1). After adding the adulthood cardiovascular risk factors (systolic blood pressure, BMI, fasting serum glucose, smoking, physical activity, and diet) to the multivariable model (Model 2), the association remained similar (Table 15, Panel C). No associations were found for the serum total cholesterol trajectories and any other cognitive domain (Tables 16 to 18). Similar to total cholesterol, the serum LDL cholesterol trajectories were inversely associated with episodic memory and associative learning, but the β estimate of the 'high-stable LDL cholesterol' group was slightly smaller compared to the β estimate of the 'high-stable total cholesterol'

trajectory group (Table 15, Panel D). Furthermore, in age, sex, and polygenic risk score-adjusted analyses (Model 1), the 'normal-increasing triglycerides' group was inversely associated with visual processing and sustained attention compared to the 'low-stable triglycerides' group (Table 16, Panel F). However, the association was diluted after adding the Model 2 covariates in the multivariable model. Additionally, no associations were found between the serum HDL cholesterol trajectory groups and any cognitive domain (Tables 15 to 18).

Overweight and obesity and cognitive performance

For BMI, an inverse dose-response association was observed with visual processing and sustained attention; the 'progressively overweight' and the 'persistently increasing obese' groups had worse visual processing and sustained attention compared to the 'stable normal weight' group in age, sex, and polygenic risk score-adjusted analyses (Model 1, Table 16, Panel G). After adding the adulthood cardiovascular risk factors (systolic blood pressure, serum total cholesterol, fasting serum glucose, smoking, physical activity, and diet) to the multivariable model (Model 2), the association remained similar (Table 16, Panel G). No associations were found between the BMI trajectory groups and other cognitive domains (Tables 15, 17, and 18).

Table 15. Associations between cardiovascular risk factor trajectories from childhood to midlife and episodic memory and associative learning (PAL test) in midlife.

Episodic memory and associative learning (PAL test)	Model 1 β estimate (95% CI)	P value	Model 2 β estimate (95% CI)	P value
A. Systolic blood pressure	N = 1,406		N = 1,389	
Normal-stable SBP	Reference		Reference	
Low-stable SBP	0.072 (-0.071–0.215)	0.323	0.075 (-0.070–0.220)	0.309
Moderate-stable SBP	-0.042 (-0.189–0.104)	0.572	-0.047 (-0.196–0.102)	0.535
Moderate-increasing SBP	-0.061 (-0.206–0.084)	0.412	-0.063 (-0.211–0.084)	0.399
Elevated-increasing SBP	-0.256 (-0.510– -0.002)	0.048	-0.262 (-0.52– -0.005)	0.046
B. Diastolic blood pressure	N = 1,404		N = 1,385	
Low-stable DBP	Reference		Reference	
Normal-stable DBP	-0.005 (-0.196–0.096)	0.499	-0.049 (-0.197–0.099)	0.517
Moderate-increasing DBP	-0.119 (-0.299–0.062)	0.196	-0.115 (-0.302–0.072)	0.227
C. Total cholesterol	N = 1,506		N = 1,489	
Low-stable total cholesterol	Reference		Reference	
Elevated-stable total cholesterol	-0.051 (-0.163–0.062)	0.378	-0.04 (-0.153–0.074)	0.494
High-stable total cholesterol	-0.238 (-0.386– -0.090)	0.002	-0.214 (-0.365– -0.064)	0.005
D. LDL cholesterol	N = 1,498		N = 1,481	
Low-stable LDL cholesterol	Reference		Reference	
Elevated-stable LDL cholesterol	-0.026 (-0.130–0.079)	0.630	-0.019 (-0.124–0.086)	0.728
High-stable LDL cholesterol	-0.195 (-0.361– -0.030)	0.021	-0.175 (-0.342– -0.009)	0.039
E. HDL cholesterol	N = 1,506		N = 1,489	
Low-stable HDL cholesterol	Reference		Reference	
Normal-stable HDL cholesterol	-0.091 (-0.223–0.042)	0.180	-0.087 (-0.222–0.048)	0.206
Elevated-stable HDL cholesterol	-0.063 (-0.215–0.088)	0.413	-0.048 (-0.205–0.109)	0.548
High-stable HDL cholesterol	-0.114 (-0.345–0.118)	0.336	-0.093 (-0.331–0.145)	0.443
F. Triglycerides	N = 1,506		N = 1,489	
Low-stable triglycerides	Reference		Reference	
Normal-increasing triglycerides	-0.073 (-0.212–0.066)	0.305	-0.065 (-0.206–0.075)	0.361
Normal-rapidly increasing	0.029 (-0.198–0.255)	0.805	0.057 (-0.178–0.292)	0.634
G. Body mass index	N = 1,575		N = 1,557	
Stable normal weight	Reference		Reference	
Stable slim	-0.038 (-0.143–0.067)	0.477	-0.055 (-0.162–0.052)	0.311
Progressively overweight	0.005 (-0.136–0.145)	0.948	0.027 (-0.116–0.170)	0.712
Persistently increasing obese	-0.194 (-0.498–0.110)	0.210	-0.207 (-0.52–0.107)	0.197

Values are β estimates, 95% CIs, and P values from linear regression models. All models were adjusted for age, sex, and polygenic risk score (Model 1). Model 2 was additionally adjusted for adulthood cardiovascular risk factors (fasting serum glucose, smoking, physical activity, and diet). For blood pressure, Model 2 were further adjusted with adulthood body mass index and adulthood serum total cholesterol. For serum lipids, Model 2 were further adjusted with adulthood body mass index and adulthood systolic blood pressure. For body mass index, Model 2 were further adjusted with adulthood systolic blood pressure and adulthood serum total cholesterol. The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

Table 16. Associations between cardiovascular risk factor trajectories from childhood to midlife and visual processing and sustained attention (RVP test) in midlife.

Visual processing and sustained attention (RVP test)	Model 1 β estimate (95% CI)	P value	Model 2 β estimate (95% CI)	P value
A. Systolic blood pressure	N = 1,492		N = 1,476	
Normal-stable SBP	Reference		Reference	
Low-stable SBP	-0.073 (-0.217–0.070)	0.318	-0.115 (-0.26–0.029)	0.118
Moderate-stable SBP	-0.033 (-0.178–0.112)	0.653	-0.003 (-0.148–0.143)	0.970
Moderate-increasing SBP	-0.201 (-0.343– -0.060)	0.005	-0.185 (-0.327– -0.043)	0.011
Elevated-increasing SBP	-0.181 (-0.420–0.057)	0.136	-0.157 (-0.396–0.082)	0.197
B. Diastolic blood pressure	N = 1,487		N = 1,471	
Low-stable DBP	Reference		Reference	
Normal-stable DBP	0.059 (-0.089–0.206)	0.435	0.068 (-0.080–0.216)	0.369
Moderate-increasing DBP	-0.099 (-0.278–0.079)	0.276	-0.067 (-0.251–0.116)	0.472
C. Total cholesterol	N = 1,601		N = 1,585	
Low-stable total cholesterol	Reference		Reference	
Elevated-stable total cholesterol	-0.014 (-0.124–0.096)	0.806	0.011 (-0.098–0.121)	0.838
High-stable total cholesterol	-0.092 (-0.237–0.054)	0.216	-0.049 (-0.195–0.097)	0.513
D. LDL cholesterol	N = 1,593		N = 1,577	
Low-stable LDL cholesterol	Reference		Reference	
Elevated-stable LDL cholesterol	-0.020 (-0.122–0.082)	0.697	0.004 (-0.098–0.105)	0.939
High-stable LDL cholesterol	0.004 (-0.160–0.167)	0.966	0.036 (-0.126–0.198)	0.660
E. HDL cholesterol	N = 1,601		N=1,585	
Low-stable HDL cholesterol	Reference		Reference	
Normal-stable HDL cholesterol	0.010 (-0.120–0.139)	0.885	-0.020 (-0.150–0.111)	0.768
Elevated-stable HDL cholesterol	0.085 (-0.063–0.232)	0.259	0.023 (-0.127–0.174)	0.763
High-stable HDL cholesterol	-0.069 (-0.295–0.157)	0.550	-0.149 (-0.378–0.081)	0.203
F. Triglycerides	N = 1,601		N = 1,585	
Low-stable triglycerides	Reference		Reference	
Normal-increasing triglycerides	-0.136 (-0.272– -0.0003)	0.049	-0.100 (-0.236–0.036)	0.149
Normal-rapidly increasing	-0.043 (-0.264–0.179)	0.705	0.052 (-0.174–0.279)	0.652
G. Body mass index	N = 1,679		N = 1,662	
Stable normal weight	Reference		Reference	
Stable slim	-0.054 (-0.158–0.049)	0.303	-0.067 (-0.171–0.038)	0.210
Progressively overweight	-0.213 (-0.350–-0.075)	0.003	-0.165 (-0.304–-0.025)	0.021
Persistently increasing obese	-0.540 (-0.835– -0.246)	0.0003	-0.407 (-0.708– -0.105)	0.008

Values are β estimates, 95% CIs, and P values from linear regression models. All models were adjusted for age, sex, and polygenic risk score (Model 1). Model 2 was additionally adjusted for adulthood cardiovascular risk factors (fasting serum glucose, smoking, physical activity, and diet). For blood pressure, Model 2 were further adjusted with adulthood body mass index and adulthood serum total cholesterol. For serum lipids, Model 2 were further adjusted with adulthood body mass index and adulthood systolic blood pressure. For body mass index, Model 2 were further adjusted with adulthood systolic blood pressure and adulthood serum total cholesterol. The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

Table 17. Associations between cardiovascular risk factor trajectories from childhood to midlife and reaction and movement time (RTI test) in midlife.

Reaction and movement time (RTI test)	Model 1 β estimate (95% CI)	P value	Model 2 β estimate (95% CI)	P value
A. Systolic blood pressure	N = 1,385		N = 1,369	
Normal-stable SBP	Reference		Reference	
Low-stable SBP	0.029 (-0.117–0.175)	0.698	0.021 (-0.126–0.168)	0.780
Moderate-stable SBP	0.139 (-0.010–0.289)	0.068	0.155 (0.003–0.306)	0.045
Moderate-increasing SBP	-0.032 (-0.180–0.117)	0.676	-0.020 (-0.169–0.129)	0.795
Elevated-increasing SBP	0.170 (-0.089–0.430)	0.199	0.197 (-0.064–0.459)	0.139
B. Diastolic blood pressure	N = 1,381		N = 1,375	
Low-stable DBP	Reference		Reference	
Normal-stable DBP	0.027 (-0.121–0.175)	0.720	0.024 (-0.124–0.173)	0.748
Moderate-increasing DBP	0.148 (-0.035–0.331)	0.113	0.165 (-0.023–0.354)	0.085
C. Total cholesterol	N = 1,482		N = 1,466	
Low-stable total cholesterol	Reference		Reference	
Elevated-stable total cholesterol	-0.029 (-0.147–0.088)	0.622	-0.026 (-0.143–0.090)	0.658
High-stable total cholesterol	-0.091 (-0.246–0.064)	0.251	-0.065 (-0.221–0.092)	0.418
D. LDL cholesterol	N = 1,474		N = 1,458	
Low-stable LDL cholesterol	Reference		Reference	
Elevated-stable LDL cholesterol	0.026 (-0.082–0.134)	0.638	0.025 (-0.082–0.133)	0.644
High-stable LDL cholesterol	-0.021 (-0.195–0.153)	0.812	-0.008 (-0.181–0.165)	0.924
E. HDL cholesterol	N = 1,482		N = 1,466	
Low-stable HDL cholesterol	Reference		Reference	
Normal-stable HDL cholesterol	-0.082 (-0.220–0.055)	0.241	-0.090 (-0.229–0.049)	0.204
Elevated-stable HDL cholesterol	-0.038 (-0.196–0.119)	0.635	-0.065 (-0.226–0.097)	0.431
High-stable HDL cholesterol	0.037 (-0.204–0.279)	0.762	0.014 (-0.232–0.260)	0.910
F. Triglycerides	N = 1,482		N = 1,466	
Low-stable triglycerides	Reference		Reference	
Normal-increasing triglycerides	-0.080 (-0.226–0.065)	0.279	-0.073 (-0.218–0.072)	0.326
Normal-rapidly increasing	-0.102 (-0.341–0.137)	0.403	-0.056 (-0.301–0.188)	0.652
G. Body mass index	N = 1,550		N = 1,533	
Stable normal weight	Reference		Reference	
Stable slim	-0.030 (-0.139–0.080)	0.595	-0.020 (-0.130–0.090)	0.717
Progressively overweight	-0.051 (-0.197–0.096)	0.497	-0.016 (-0.164–0.132)	0.836
Persistently increasing obese	-0.285 (-0.602–0.033)	0.079	-0.305 (-0.63–0.020)	0.065

Values are β estimates, 95% CIs, and P values from linear regression models. All models were adjusted for age, sex, and polygenic risk score (Model 1). Model 2 was additionally adjusted for adulthood cardiovascular risk factors (fasting serum glucose, smoking, physical activity, and diet). For blood pressure, Model 2 were further adjusted with adulthood body mass index and adulthood serum total cholesterol. For serum lipids, Model 2 were further adjusted with adulthood body mass index and adulthood systolic blood pressure. For body mass index, Model 2 were further adjusted with adulthood systolic blood pressure and adulthood serum total cholesterol. The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

Table 18. Associations between cardiovascular risk factor trajectories from childhood to midlife and short-term working memory (SWM test) in midlife.

Short-term working memory (SWM test)	Model 1 β estimate (95% CI)	P value	Model 2 β estimate (95% CI)	P value
A. Systolic blood pressure	N = 1,519		N = 1,502	
Normal-stable SBP	Reference		Reference	
Low-stable SBP	0.014 (-0.125–0.154)	0.840	0.030 (-0.112–0.171)	0.679
Moderate-stable SBP	-0.072 (-0.213–0.069)	0.316	-0.085 (-0.229–0.058)	0.245
Moderate-increasing SBP	-0.056 (-0.194–0.082)	0.427	-0.061 (-0.201–0.079)	0.396
Elevated-increasing SBP	-0.146 (-0.378–0.087)	0.220	-0.165 (-0.401–0.071)	0.170
B. Diastolic blood pressure	N = 1,514		N = 1,497	
Low-stable DBP	Reference		Reference	
Normal-stable DBP	0.134 (-0.009–0.276)	0.066	0.120 (-0.025–0.265)	0.103
Moderate-increasing DBP	0.055 (-0.118–0.229)	0.530	0.026 (-0.153–0.206)	0.774
C. Total cholesterol	N = 1,630		N = 1,613	
Low-stable total cholesterol	Reference		Reference	
Elevated-stable total cholesterol	-0.099 (-0.207–0.010)	0.075	-0.091 (-0.200–0.019)	0.104
High-stable total cholesterol	-0.077 (-0.220–0.066)	0.292	-0.068 (-0.213–0.077)	0.358
D. LDL cholesterol	N = 1,622		N = 1,605	
Low-stable LDL cholesterol	Reference		Reference	
Elevated-stable LDL cholesterol	-0.024 (-0.124–0.077)	0.644	-0.026 (-0.127–0.075)	0.610
High-stable LDL cholesterol	-0.018 (-0.178–0.142)	0.824	-0.017 (-0.178–0.144)	0.836
E. HDL cholesterol	N = 1,630		N = 1,613	
Low-stable HDL cholesterol	Reference		Reference	
Normal-stable HDL cholesterol	-0.014 (-0.141–0.114)	0.835	0.003 (-0.127–0.133)	0.962
Elevated-stable HDL cholesterol	-0.054 (-0.199–0.091)	0.466	-0.029 (-0.179–0.121)	0.707
High-stable HDL cholesterol	-0.161 (-0.383–0.061)	0.155	-0.124 (-0.353–0.104)	0.285
F. Triglycerides	N = 1,630		N = 1,613	
Low-stable triglycerides	Reference		Reference	
Normal-increasing triglycerides	-0.003 (-0.136–0.131)	0.966	-0.007 (-0.142–0.129)	0.924
Normal-rapidly increasing	0.006 (-0.212–0.224)	0.955	-0.012 (-0.237–0.214)	0.919
G. Body mass index	N = 1,711		N = 1,693	
Stable normal weight	Reference		Reference	
Stable slim	-0.05 (-0.151–0.051)	0.333	-0.064 (-0.167–0.039)	0.224
Progressively overweight	0.013 (-0.121–0.147)	0.849	0.029 (-0.109–0.166)	0.683
Persistently increasing obese	0.065 (-0.222–0.352)	0.656	0.151 (-0.146–0.448)	0.318

Values are β estimates, 95% CIs, and P values from linear regression models. All models were adjusted for age, sex, and polygenic risk score (Model 1). Model 2 was additionally adjusted for adulthood cardiovascular risk factors (fasting serum glucose, smoking, physical activity, and diet). For blood pressure, Model 2 were further adjusted with adulthood body mass index and adulthood serum total cholesterol. For serum lipids, Model 2 were further adjusted with adulthood body mass index and adulthood systolic blood pressure. For body mass index, Model 2 were further adjusted with adulthood systolic blood pressure and adulthood serum total cholesterol. The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

5.6 Cardiovascular risk factor accumulation and cognitive performance

Inverse linear trends were observed for episodic memory and associative learning (PAL test: β = -0.068 SD, P = 0.026 for trend), visual processing and sustained attention (RVP test: β = -0.139 SD, P<0.0001 for trend), and reaction and movement time (RTI test: β = -0.078 SD, P = 0.015 for trend) in the age sex, and polygenic risk score-adjusted analyses for the cardiovascular risk factor score (Model 1). After adding adulthood fasting serum glucose, smoking, physical activity, and diet as covariates to the multivariable model (Model 2), the associations remained essentially similar (PAL test: β = -0.084 SD, P = 0.008 for trend; RVP test: β = -0.125 SD, P<0.0001 for trend; RTI test: β = -0.064 SD, P = 0.048 for trend). The trend was nonsignificant for short-term working memory (SWM test: β = 0.014 SD, P = 0.638 in Model 1 and β = 0.014 SD, P = 0.636 in Model 2).

To analyze the increasing cardiovascular risk factor score, the group without any cardiovascular risk factors was used as the reference group. An inverse age, sex, and polygenic risk score-adjusted association was observed between episodic memory and associative learning for three cardiovascular risk factors, on visual processing and sustained attention for two and three cardiovascular risk factors, and on reaction and movement time for two cardiovascular risk factors (Table 19, Model 1). After adding adulthood fasting serum glucose, smoking, physical activity, and diet as covariates to the multivariable model (Model 2), the association diluted only marginally (Table 19). No associations were found for short-term working memory.

Table 19. Association between cardiovascular risk factor score and cognitive performance in midlife.

Cardiovascular risk factor score	Model 1 β estimate (95% CI)	P value	Model 2 β estimate (95% CI)	P value
Episodic memory and associative learning (PAL test; N = 1,551)				
0	Reference		Reference	
1	-0.062 (-0.169–0.045)	0.256	-0.069 (-0.176–0.038)	0.207
2	-0.104 (-0.250–0.043)	0.166	-0.128 (-0.277–0.020)	0.090
3	-0.305 (-0.600– -0.010)	0.043	-0.390 (-0.691– -0.088)	0.011
Visual processing and sustained attention (RVP test; N = 1,656)				
0	Reference		Reference	
1	-0.104 (-0.208–0.001)	0.051	-0.097 (-0.202–0.007)	0.068
2	-0.271 (-0.414– -0.127)	0.0002	-0.241 (-0.386– -0.095)	0.001
3	-0.488 (-0.768– -0.208)	0.001	-0.443 (-0.730– -0.157)	0.003

Cardiovascular risk factor score	Model 1 β estimate (95% CI)	P value	Model 2 β estimate (95% CI)	P value
Reaction and movement time (RTI test; N = 1,527)				
0	Reference		Reference	
1	-0.053 (-0.163–0.058)	0.351	-0.046 (-0.156–0.064)	0.411
2	-0.199 (-0.353– -0.046)	0.011	-0.164(-0.318– -0.010)	0.037
3	-0.152 (-0.459–0.154)	0.331	-0.122 (-0.434–0.190)	0.442
Short-term working memory (SWM test; N = 1,687)				
0	Reference		Reference	
1	0.067 (-0.035–0.170)	0.198	0.066 (-0.036–0.169)	0.205
2	-0.016 (-0.156–0.125)	0.827	-0.014 (-0.156–0.128)	0.846
3	0.082 (-0.195–0.359)	0.560	0.081 (-0.204–0.365)	0.578

Values are β estimates, 95% CIs, and P values are from linear regression models. Model 1 was adjusted for age, sex, and polygenic risk score. Model 2 was also adjusted for adulthood cardiovascular risk factors (fasting serum glucose, smoking, physical activity, and diet). The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Modified from the original publication II in the Circulation with permission of Wolters Kluwer Health, Inc.

5.7 Serum creatinine and cognitive performance (III)

5.7.1 Serum creatinine trajectories characteristics

In men and women, consistently low serum creatinine levels were associated with poor childhood school performance, low education, low annual income, low physical activity, and smoking. Additionally, low serum creatinine was associated with higher antihypertensive medication use and higher systolic blood pressure in men, while in women, low serum creatinine was associated with higher BMI and triglyceride levels. The descriptive characteristics of the serum creatinine trajectory groups in the 2001 and 2011 follow-ups are presented in detail, separately for men and women, in the original publication of Study III.

5.7.2 Serum creatinine trajectories and cognitive performance

In men, serum creatinine was directly associated with overall cognitive performance and short-term working memory (SWM test). The ‘high serum creatinine’ group had better overall cognitive performance and short-term working memory compared with the ‘low serum creatinine’ group in the age, childhood school performance, and education-adjusted analyses (Table 20, Model 1). Additionally, serum creatinine showed a weak direct association with episodic memory and associative learning (PAL test); the ‘normal serum creatinine’ and ‘moderate serum creatinine’ groups had better episodic memory and associative learning compared with the ‘low serum creatinine’ group in the age,

childhood school performance, and education-adjusted analyses (Table 20, Model 1). After adding APOE, systolic blood pressure, serum total cholesterol, BMI, smoking, physical activity, diet, antihypertensive medication, and diabetes and impaired fasting glucose to the multivariable model (Model 2), the associations for both short-term working memory and episodic memory and associative learning became stronger (Table 20). No associations were found for women (Table 21).

Table 20. Associations between serum creatinine trajectories and midlife cognitive performance in men.

	Model 1 **β estimate (95% CI)**	**P value**	**Model 2** **β estimate**	**P value**
Short-term working memory (SWM test)				
	N = 681		N = 670	
Low creatinine	Reference		Reference	
Moderate creatinine	0.097 (-0.107–0.301)	0.349	0.125 (-0.085–0.335)	0.244
Normal creatinine	0.100 (-0.118–0.318)	0.369	0.140 (-0.086–0.366)	0.224
High creatinine	0.328 (0.017–0.638)	0.039	0.349 (0.031–0.667)	0.031
Episodic memory and associative learning (PAL test)				
	N = 628		N = 616	
Low creatinine	Reference		Reference	
Moderate creatinine	0.212 (-0.003–0.426)	0.053	0.251 (0.030–0.472)	0.026
Normal creatinine	0.217 (-0.011–0.445)	0.062	0.239 (0.003–0.476)	0.047
High creatinine	0.205 (-0.107–0.517)	0.198	0.251 (-0.068–0.570)	0.123
Reaction and movement time (RTI test)				
	N = 617		N = 606	
Low creatinine	Reference		Reference	
Moderate creatinine	-0.097 (-0.329–0.135)	0.412	-0.154 (-0.391–0.083)	0.202
Normal creatinine	0.050 (-0.196–0.296)	0.691	0.005 (-0.248–0.258)	0.970
High creatinine	0.047 (-0.295–0.390)	0.786	-0.037 (-0.384–0.310)	0.835
Visual processing and sustained attention (RVP test)				
	N = 670		N = 659	
Low creatinine	Reference		Reference	
Moderate creatinine	-0.040 (-0.243–0.163)	0.700	-0.063 (-0.271–0.145)	0.552
Normal creatinine	0.024 (-0.193–0.241)	0.827	-0.022 (-0.246–0.202)	0.845
High creatinine	0.060 (-0.250–0.370)	0.703	0.027 (-0.288–0.343)	0.864

Values are β estimates, 95% CIs, and P values from linear regression models. All models were adjusted for age, childhood school performance, and education (Model 1). Model 2 was additionally adjusted for APOE, systolic blood pressure, serum total cholesterol, body mass index, smoking, physical activity, diet, antihypertensive medication, and diabetes and impaired fasting glucose. The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Reproduced from the original publication III in the Neurology with permission of Wolters Kluwer Health, Inc.

The possible effect modification was studied for those cognitive domains that showed association with the serum creatinine trajectories (i.e., short-term working memory and episodic memory and associative learning) in men by introducing multiplicative interaction terms for each possible modifier (e.g., age * serum creatinine groups) separately to the fully adjusted linear regression models (Model 2). No significant interactions were found.

Table 21. Associations between serum creatinine trajectories and midlife cognitive performance in women.

	Model 1 **β estimate (95% CI)**	**P value**	**Model 2** **β estimate**	**P value**
Short-term working memory (SWM test)				
	N = 890		N = 879	
Low creatinine	Reference		Reference	
Moderate creatinine	-0.048 (-0.263–0.167)	0.661	-0.046 (-0.262–0.171)	0.677
Normal creatinine	-0.057 (-0.284–0.169)	0.619	-0.046 (-0.275–0.182)	0.691
High creatinine	-0.020 (-0.283–0.243)	0.882	-0.054 (-0.318–0.209)	0.687
Episodic memory and associative learning (PAL test)				
	N = 813		N = 805	
Low creatinine	Reference		Reference	
Moderate creatinine	0.099 (-0.134–0.332)	0.405	0.088 (-0.154–0.323)	0.460
Normal creatinine	-0.126 (-0.369–0.118)	0.311	-0.109 (-0.354–0.136)	0.384
High creatinine	0.145 (-0.136–0.427)	0.312	0.153 (-0.129–0.435)	0.286
Reaction and movement time (RTI test)				
	N = 803		N = 795	
Low creatinine	Reference		Reference	
Moderate creatinine	0.059 (-0.175–0.292)	0.621	0.016 (-0.218–0.249)	0.895
Normal creatinine	0.072 (-0.172–0.316)	0.565	0.010 (-0.234–0.254)	0.936
High creatinine	-0.111 (-0.393–0.170)	0.438	-0.147 (-0.428–0.133)	0.303
Visual processing and sustained attention (RVP test)				
	N = 869		N = 858	
Low creatinine	Reference		Reference	
Moderate creatinine	0.122 (-0.091–0.335)	0.263	0.112 (-0.103–0.323)	0.307
Normal creatinine	0.075 (-0.150–0.299)	0.514	0.051 (-0.174–0.277)	0.655
High creatinine	0.115 (-0.146–0.377)	0.386	0.111 (-0.150–0.372)	0.406

Values are β estimates, 95% CIs, and P values from linear regression models. All models were adjusted for age, childhood school performance, and education (Model 1). Model 2 was additionally adjusted for APOE, systolic blood pressure, serum total cholesterol, body mass index, smoking, physical activity, diet, antihypertensive medication, and diabetes and impaired fasting glucose. The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing. Reproduced from the original publication III in the Neurology with permission of Wolters Kluwer Health, Inc.

5.8 Risk factors linking to cognitive aging (I–III)

To bring clinical interpretability to the results, the association between cognitive performance and cardiovascular risk factors, physical activity, and serum creatinine were transformed to correspond with the effect of aging, i.e., converted into the perspective of 'cognitive aging.' For this transformation, the β estimates for the risk factors that showed association in the test-specific fully adjusted multivariable models (Models 2 from studies I, II, and III) were compared with the β estimates of age. Specifically, the difference in cognitive aging was estimated by dividing the β estimates of the risk factors by the β estimates of age from the same statistical model. The β estimates of age are presented in Table 22, and the differences in cognitive aging in Figure 10.

For example, for visual processing and sustained attention, the group with three cardiovascular risk factors had a 6.9-year higher cognitive age than the group without any cardiovascular risk factors (Figure 10). For reaction and movement time, the β estimates of participants being physically active in childhood corresponded with a 5.2-year lower cognitive age in midlife.

Table 22. Effect estimates of age.

	β estimate of age
Episodic memory and associative learning (PAL test)	
Elevated-increasing systolic blood pressure	-0.051
High-stable total cholesterol	-0.053
High-stable LDL cholesterol	-0.052
3 cardiovascular risk factors	-0.056
Moderate creatinine in men	-0.050
Normal creatinine in men	-0.050
Short-term working memory (SWM test)	
High creatinine in men	-0.042
Reaction and movement time (RTI test)	
Physical activity in childhood	-0.007
Physical activity in adolescence	-0.006
Physical activity in young adulthood	-0.004
Physical activity in adulthood	-0.007
2 cardiovascular risk factors	-0.009
Visual processing and sustained attention (RVP test)	
Moderate-increasing systolic blood pressure	-0.025
Progressively overweight	-0.021
Persistently increasing obese	-0.021
2 cardiovascular risk factors	-0.022
3 cardiovascular risk factors	-0.022

Values are β estimates of age from the test-specific fully adjusted multivariable models (Models 2 from studies I, II, and III). The Cambridge Neuropsychological Test Automated Battery (CANTAB®) was used for cognitive testing.

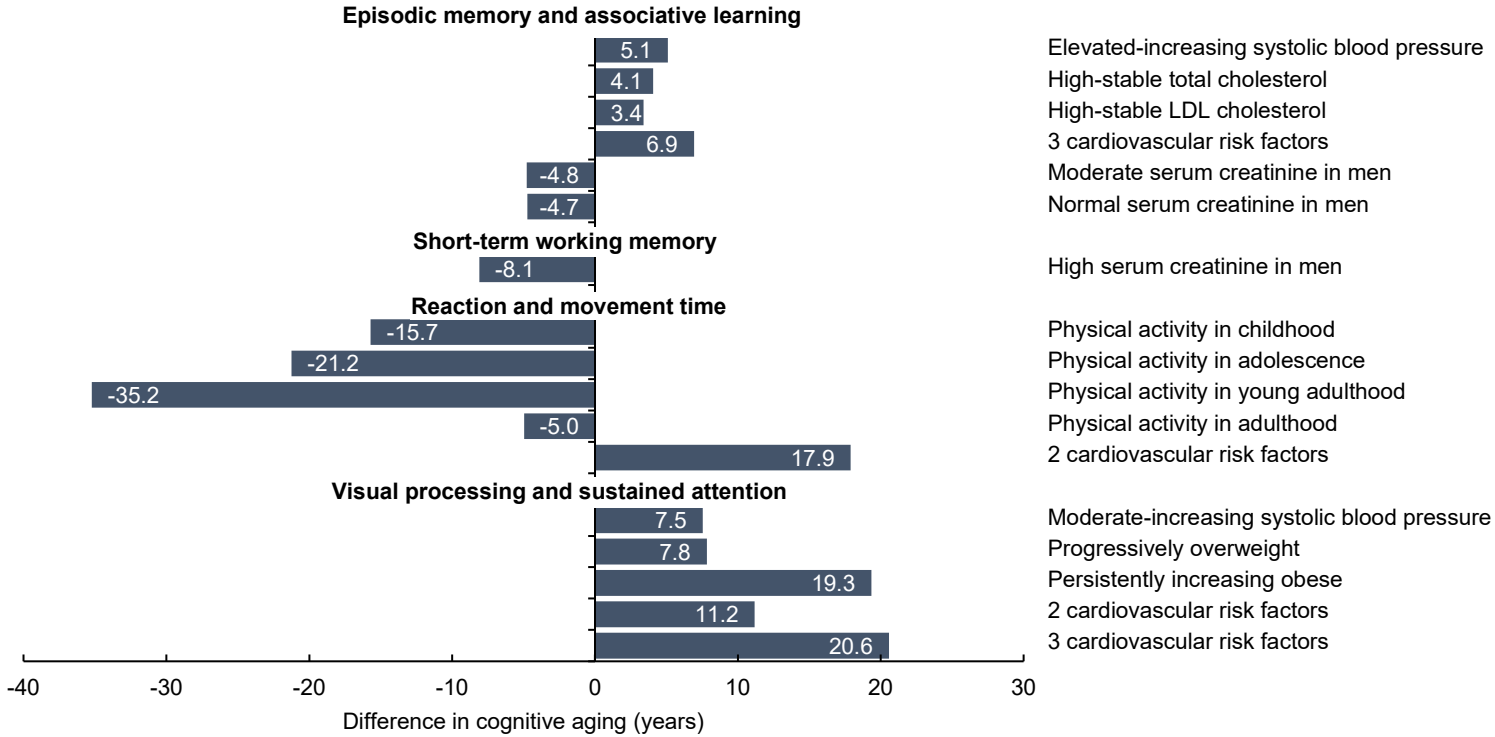

Figure 10. The differences of cognitive aging for cardiovascular risk factors, physical activity, and serum creatinine.

6 Discussion

6.1 Physical activity accumulation and cognitive performance

The main results of Study I indicate that higher physical activity accumulation in early life is associated with faster reaction and movement time in midlife. This association was observed in all early life groups representing childhood, adolescence, and young adulthood. In addition, higher physical activity accumulation in adulthood was observed to be associated with faster reaction and movement time. The associations remained robust despite the wide adjustments that were used to control the models: age, sex, childhood SES, childhood school performance, education, adulthood systolic blood pressure, total cholesterol, and BMI. It is important to note that all the associations for early life and adulthood physical activity accumulation remained significant even when the other age windows were taken into account.

Furthermore, among men, a weak association was observed between physical activity accumulation and visual processing and sustained attention during adolescence, young adulthood, and adulthood. However, the associations diluted after taking, for example, childhood school performance and adulthood education into account.

These observations are in line with that of the previous prospective [7,130–133,136,142,143] and cross-sectional [137] studies that reported associations between higher physical activity and better cognitive performance among adolescents [136,137] and adults or older-aged cohorts [7,130–133,142,143]. These results are also supported by previous studies that retrospectively assessed physical activity in relation to better old age cognitive performance [138–140]. Furthermore, a similar association between higher physical activity and faster reaction time was reported in a cross-sectional cohort of 241 participants aged between 15 and 71 years [225]. In that study, higher physical activity was found to be associated with faster reaction time only among the older half of the cohort where the mean age was 50.

Previous studies have observed that higher physical activity is associated with better executive function [7,130–132,138,142,143], better memory [131–133,142], or faster processing speed [7,131,139]. The previous retrospective studies have

highlighted the possible importance of early life physical activity, as physical activity in teenage [138], from 15 to 25 years [139], and during the whole life-course, especially in early life [140], were related to better cognitive performance in old-age. Only in one prior prospective study was physical activity since childhood (from the age of 11) assessed and linked to cognitive performance at the age of 50 [142]. However, the association of early life physical activity was observed, but physical activity in adulthood or the childhood level of cognitive function were not considered possible confounders. These limitations weaken the possibility of interpreting the independent carry-over associations of early life physical activity for midlife cognitive performance. The observations from Study I thus complement this gap in knowledge.

In Study I, no association was observed between physical activity and memory functions, which however, has been reported by several previous studies with older cohorts. It can be hypothesized that the association between physical activity and memory and executive function exerts its influence from adulthood or from early midlife, which is supported by the findings observed in the CARDIA study [7] and the British 1946 birth cohort study [133]. However, some previous studies observed no association between retrospectively assessed early life physical activity [141] or prospectively assessed physical activity in midlife [129,134] and cognitive performance or the risk of dementia. It thus raises some uncertainties about the causal relations between physical activity and cognitive performance. In conclusion, having a physically active lifestyle should be encouraged from childhood, adolescence, and young adulthood, and should be continued to midlife to ensure its plausible benefits on adulthood cognitive performance.

Potential mechanisms

There are several potential mechanisms for the association between physical activity and cognitive performance. Increased neurogenesis induced by physical activity has been suggested as the biological link to better cognitive performance [226]. In addition, increased neuronal plasticity and upregulated secretion of neurotrophic factors are plausible links in physically active individuals [227]. A higher level of physical activity has also been associated with increased secretion of brain-derived neurotrophic factor [228], which is involved in neuroplasticity, neurogenesis, neuronal survival, synaptogenesis, and energy homeostasis regulation [229]. Hence, brain-derived neurotrophic factor has been suggested as a biological mediator between physical activity and cognitive performance. It may thus has a key role in maintaining or improving cognitive performance [230,231].

In the vascular hypothesis, it has been suggested that physical activity improves cardiovascular risk factor levels, such as high blood pressure and elevated total

cholesterol, which might be the reason for its association with cognitive performance [231,232]. Furthermore, physical inactivity is suggested to compromise cerebral vascular structure and function, which may cause endothelial dysfunction and lead to a reduced capability to maintain the blood flow demands of the brain [23], which could also subsequently affect cognitive performance. Additionally, reduction in stress and anxiety, reduced inflammation, and improved insulin sensitivity are suggested as the other possible mechanisms for the association between physical activity and cognitive performance [231].

In addition, it can be hypothesized that physical activity may increase not only cognitive performance but also the neural activity in the brain areas linked to the regulation of physical activity behavior, such as the hippocampus. Hence, improved cognitive performance could further increase physical activity and, ultimately, induce a reinforcing positive loop between physical activity and cognitive performance. Neurogenesis is thus increased, and life-course cardiovascular health improved and, eventually, the risk of dementia may be decreased.

Experimental evidence from animal studies supports the causal relationship between physical activity and cognitive performance. Similar to the observational findings in humans, the previous studies focused on adult [233], middle age [230] and old rodents [234] have indicated that higher physical activity may be associated with better spatial learning. Supporting the present thesis' findings on the role of childhood physical activity in adulthood cognitive performance, an experimental study on rats found a beneficial role of childhood physical activity on neurodevelopment [235], a finding that suggests that early life exercise may induce more complex neural circuitry development by adulthood and result in a greater tolerance of later brain damage. It might thus be hypothesized that early life physical activity may be associated with better cognitive performance in midlife in humans as well.

6.1.1 Limitations of physical activity studies

In previous studies, either in the Young Finns Study or other cohorts, physical activity was assessed using self-reported questionnaires. Self-reported questionnaires may be limited by their lack of reliability or validity [236]. This might cause reporting bias, which may be especially pronounced in studies that retrospectively assess physical activity. However, in the Young Finns Study, the self-reported physical activity questionnaires were validated using an average number of daily pedometer steps, suggesting the physical activity data's good validity [208–210].

Another important limitation in relation to physical activity is reverse causation. Some previous studies have suggested that low physical activity may be caused by

poor cognitive performance [134]. Moreover, in the Whitehall II cohort study, no association was observed between midlife physical activity and old-age cognitive performance or the risk of dementia [129]. Instead, it was reported that physical activity levels started to decline approximately nine years before the dementia diagnosis. The authors of that study noted that the observation differs significantly from the observation in previous literature. It is important also to note that in Whitehall II, the participants' mean age was 45 years at baseline, meaning that it is possible that the neuropathological process causing cognitive deficits and dementia could be already ongoing on the participants at the time of baseline examinations. The results of the present thesis thus highlight the importance of independent early life physical activity on midlife cognitive performance.

In addition to previous prospective studies, randomized clinical trials have indicated the beneficial role of higher physical activity in cognitive performance, as higher physical activity in childhood has been related to better childhood cognitive performance, and higher physical activity in older age has been related to better cognitive performance [124]. Furthermore, previous studies that used experimental models have indicated that higher physical activity is causally linked to better cognitive performance [230,233–235].

6.2 Blood pressure

The main result of this thesis indicates that consistently high systolic blood pressure since childhood is associated with poorer episodic memory and associative learning as well as with worse visual processing and sustained attention in midlife. The associations were found to be significant even after controlling for a wide range of covariates, including age, sex, polygenic risk score, and adulthood cardiovascular risk factors (total cholesterol, BMI, fasting glucose, smoking, physical activity, and diet). Furthermore, in the original publication II, the observations were additionally controlled for childhood school performance, education, and childhood SES, and the associations remained essentially similar. A similar association was not observed for diastolic blood pressure.

The results of the association between high systolic blood pressure and worse cognitive performance are in line with the results of previous prospective studies conducted on adults [61], middle-aged [58,59,62], and old-aged [60] individuals. These studies observed that elevated systolic blood pressure is associated with poorer memory [58,60–62], slower processing speed [58,59,61,62], or worse executive function [59,61]. It is important to note that, in the present thesis, similar cognitive domain-specific findings were observed, as consistently high systolic blood pressure since childhood was found to be associated with poorer episodic memory and associative learning as well as worse visual processing and sustained attention. These

observations thus indicate that the harmful role of high systolic blood pressure may start to influence cognitive performance earlier than believed.

The CARDIA study is the only previous observational cohort with its follow-up time starting from young adulthood (age range at baseline between 18 and 30 years) [61]. Moreover, the Young Finns Study has the potential to focus on even earlier time windows during one's lifespan, as it covers the important age windows of childhood and adolescence, with its participants aged between three and 18 years at baseline examinations. Unfortunately, no other prospective cohorts since childhood exist where the plausible role of early life blood pressure levels on later life cognitive performance could be studied. In this thesis, systolic blood pressure was modeled from childhood to midlife using trajectory modeling. In the modeling, high systolic blood pressure was observed to occur in two separate groups. In one group, systolic blood pressure was already high in childhood and remained consistently high until midlife. In another group, systolic blood pressure was observed to be normal in childhood, but continuously increasing blood pressure levels were observed from youth to midlife. Consistently high systolic blood pressure was associated with poorer episodic memory and associative learning, while continuously increasing systolic blood pressure was associated with worse visual processing and sustained attention. The present findings thus complement the earlier observation from the Young Finns Study, where high systolic blood pressure in early life was observed to be associated with poorer episodic memory and associative learning, while no association was observed between early life systolic blood pressure and visual processing and sustained attention [64]. It can thus be hypothesized that high systolic blood pressure starts influencing learning and memory from childhood, but its influence on processing speed may start later during young adulthood.

Previous studies have also longitudinally modeled cardiovascular risk factors. Using a similar trajectory modeling as in this thesis to identify blood pressure trajectories, the CARDIA study identified five groups for systolic and diastolic blood pressure [237]. This is a departure from this thesis, which identified only three diastolic blood pressure groups. The visual comparison of the systolic blood pressure trajectory models between the CARDIA study and this thesis looks virtually similar. The shape of the five different groups in systolic blood pressure is also similar, but there is a difference in the increasing systolic blood pressure group. In the CARDIA study, systolic blood pressure starts increasing after the age of 30, while in the Young Finns Study, systolic blood pressure elevates in adolescence. For this difference, there are several potential reasons. The CARDIA study was conducted with participants from the US, and its baseline study was conducted when the participants were aged between 18 and 30. The participants in the Young Finns Study were thus approximately 15 years younger at the baseline examinations. It might be hypothesized that participants with better general health at the time of baseline

examinations participated in the CARDIA study clinical examinations, while in the Young Finns Study, the younger participants at baseline resulted in a study population that is less selected and thus more representative of the general population.

There are several potential mechanisms for the association between high blood pressure and poorer cognitive performance. In experimental studies, the blood–brain barrier disruption has been suggested as a causal link between high blood pressure and worse cognitive performance [238]. In a study conducted on rats, high blood pressure was found to increase the leakage of serum components from small arterioles into the hippocampus through the impaired blood–brain barrier [238]. Furthermore, long-term hypertension has been related to increased arterial stiffness, which might possibly lead to ischemic conditions [62]. However, the detailed mechanisms for this association remain uncertain.

6.3 Serum lipids

The main results of this thesis indicate that consistently high total and LDL cholesterol levels since childhood are associated with poorer episodic memory and associative learning in midlife. Even after a wide range of covariates—age, sex, polygenic risk score, and adulthood cardiovascular risk factors (systolic blood pressure, BMI, fasting glucose, smoking, physical activity, and diet)—were controlled, the association remained robust. Moreover, in the original publication II, even when the observation was additionally controlled for childhood school performance, education, and childhood SES, the association remained essentially similar.

These observations are in line with those of previous prospective studies conducted on adults [61,72], middle-aged [71,72], and old-aged [70,72] individuals, that reported an association between serum lipids and cognitive performance. Out of these studies, only one examined the associations of other lipids and observed an inverse association between cognitive performance and total cholesterol, LDL cholesterol, and triglycerides [71]. According to previous studies, higher total cholesterol is related to poorer memory [61,71,72], worse executive function [70–72], or reduced sustained attention [70,71]. The present results indicate an inverse association between high total and LDL cholesterol and episodic memory and associative learning. This observation, which is similar to that of previous studies, suggests a plausible and important role for early life total and LDL cholesterol levels in adulthood cognitive performance.

The total and LDL cholesterol were modeled from childhood to midlife using trajectory modeling. The model identified three distinct groups from the whole study population for both total and LDL cholesterol. For example, the participants' total

cholesterol concentration from childhood to midlife was consistently close to 6 mmol/l in the highest total cholesterol group, consistently close to 5 mmol/l in the middle group, and consistently close to 4 mmol/l in the lowest group. The inverse association between total cholesterol and episodic memory and associative learning was observed only for the highest total cholesterol group when compared to the participants in the lowest total cholesterol group. Achieving AHA's definition for an ideal total cholesterol—<5.172 mmol/l [94]—might thus be important to consider from childhood in relation to adulthood cognitive health.

The importance of early life high cholesterol levels has been highlighted by a previous report from the Young Finns Study, where higher LDL cholesterol in childhood was observed to be associated with poorer episodic memory and associative learning in midlife [64]. The findings of this thesis thus complement those of this previous report. Furthermore, the β estimates in this thesis were higher for total cholesterol than for LDL cholesterol, which may underline that total cholesterol has a central role in cognitive performance. However, as no associations were observed for HDL cholesterol or triglycerides, an adverse association for high total cholesterol might be mainly mediated via LDL cholesterol.

Furthermore, previous studies have used trajectory modeling to examine serum lipids longitudinally. In the Framingham Offspring Study, three trajectory groups were identified for non-HDL cholesterol between the ages of 30 and 65 years [239]. In that study, a similar method was used as in the present thesis, and the shapes of the non-HDL cholesterol groups until the age of 50 years corresponded to the present thesis' total cholesterol and LDL cholesterol groups. After the age of 50, the non-HDL cholesterol levels in the highest group started to decline.

The potential mechanism for the association between adverse serum lipids and cognitive performance is uncertain. As a neuropathological mechanism, high total cholesterol and LDL cholesterol are suggested to increase neuritic plaques (which are suggested to induce the formation of beta-amyloid plaques) in both the neocortex and the hippocampal/entorhinal region [240]. Experimental evidence supports the causal role of hypercholesterolemia in cognitive performance. In rats, hypercholesterolemia has been found to be associated with memory impairment, cholinergic dysfunction, inflammation, enhanced cortical beta-amyloid and tau protein accumulation, and microbleedings, all of which have a role in Alzheimer's disease pathology [241]. Further supporting findings have been reported in a study conducted on mice, where hypercholesterolemia was found to be associated with increased neuroinflammation and amyloid precursor protein [242]. However, further research is required to uncover the detailed mechanisms.

6.4 Obesity and overweight

This thesis' main results indicate that overweight and obesity from childhood are associated with worse visual processing and sustained attention in midlife in a dose-responsive manner. Even after taking into account a wide range of covariates—age, sex, polygenic risk score, and adulthood cardiovascular risk factors (systolic blood pressure, total cholesterol, fasting glucose, smoking, physical activity, and diet)—the associations were robust. In the original publication II, even when the observations were additionally controlled for childhood school performance, education, and childhood SES, the associations remained essentially similar.

The finding of the association of overweight and obesity with worse cognitive performance is in line with previous prospective studies conducted on adolescents or adults [78,80,81], middle-aged [77–79], and old-aged [60] individuals. Previous studies used either BMI [60,77,78,80,81], waist-to-hip ratio [78], or waist circumference [79] to assess adiposity, overweight, and obesity, observing that overweight and obesity are associated with poorer memory [60,78,80,81], slower processing speed [77,79–81], or worse executive function [80]. A similar cognitive domain-specific finding was thus observed in this thesis, as both overweight and obesity since childhood were associated with worse visual processing and sustained attention in a dose-responsive manner.

Trajectory modeling was used to longitudinally model BMI from childhood to midlife. The modeling identified four distinct BMI groups, of which two groups gained weight continuously from childhood to midlife. In one of these two groups, the participants had a BMI close to or over 30 kg/m^2, while the participants in the other group had a BMI up to 40 kg/m^2 in midlife. This highlights the importance of more aggressive means for preventing obesity since childhood, as obesity is known to influence cardiovascular health and also importantly, as shown in this thesis, cognitive health much earlier than believed.

BMI trajectories have been previously reported in the Young Finns Study population [243], where six distinct trajectory groups were identified for BMI. Three trajectory groups were identified for overweight and obese BMI levels, while two groups were identified in this thesis. Additionally, a smaller minimum group size was allowed, which resulted in the identification of 43 participants who lost weight from overweight to normal weight after the age of 30. This group was not observed in this thesis, probably because the group sizes were preferred to be >5% of the whole study population to meaningfully analyze cognitive performance. It is thus possible that these individuals with fluctuating BMI levels might have been categorized into a trajectory group with close to normal weight in this thesis. Moreover, due to trajectory modeling, it was not possible in this thesis to focus on the association of losing weight with cognitive performance.

The mechanisms capable of explaining the association between obesity and overweight on cognitive performance or risk of dementia are unclear. It is hypothesized that lifestyle factors—diet, smoking, alcohol consumption, and physical activity—may interact with obesity and thus modify the association between obesity and the risk of dementia [75]. Obesity is also a risk factor for cardiovascular diseases and may thus influence cognitive performance indirectly via cardiovascular risk factors and diseases. Other hypotheses regarding the underlying mechanisms are suggested to be secretions of adipose tissue, such as hormones, cytokines, and growth factors [80]. These various bioactive metabolites include insulin-like growth factor-I, transforming growth factor β, tumor necrosis factor α, angiotensin II, leptin, neurotrophins, fatty acids, and many other factors that may cross the blood–brain barrier, affect brain metabolism, and subsequently cause dementia [244]. Furthermore, obesity's causal relationship with cognitive performance is supported by the existing experimental evidence. In a study conducted on mice, diet-induced adiposity and weight gain without physical exercise were found to be associated with poorer cognitive performance [245]. In another study conducted on mice [246], overweight was caused by a high-fat diet in young mice during a 15-week period. Afterwards, a normal low-fat diet was continued, and body weight returned to normal. However, being overweight in early life was observed to be associated with poor learning and memory as well as synaptic impairment in the adult mice's hippocampus. This study supports the view that, independent of adulthood weight status, childhood overweight might contribute to adulthood cognitive performance.

6.5 Limitations of blood pressure, serum lipids, and obesity and overweight studies

A significant limitation of the studies that examined the associations between individual cardiovascular risk factors and cognitive performance is that they did not take into account cardiovascular risk factor accumulation. Most of the previous studies focused on the effect of a single risk factor in relation to cognitive performance or risk of dementia, usually considering other cardiovascular risk factor covariates. According to the Lancet Commission, even controlling other cardiovascular risk factors does not fully take into account the combinations and contexts in which risk occurs [3]. However, in the Lancet Commission's statement, risk factor accumulation is not listed as a potentially modifiable risk factor for dementia, which might be mainly because of the lack of studies on risk factor accumulation. Furthermore, it is important to note that risk factor accumulation was studied for the first time from childhood to midlife in the Young Finns Study.

Another significant limitation of previous studies is their assessment of risk factors. Most of them examined risk factors at a single time point (e.g., in midlife) and cognitive performance after a varying time of follow-up or cross-sectionally. It has been shown that longitudinal risk factor levels have a better predictive ability than a model that uses only the most recent measurement information concerning cardiovascular risk factors [247]. Furthermore, the previous data with risk factor assessment at a single time point do not allow the researchers to consider the exposure time or the potentially critical age windows for exposure when the adverse risk factor levels might have a higher influence on cognitive health, such as growth and maturation in adolescents.

This thesis' potential limitation is its trajectory modeling method, which was used to model cardiovascular risk factor levels from childhood to midlife. Trajectory modeling is a data-driven method in which all available data is used and no a priori hypothesis is applied. Trajectory modeling thus allows longitudinal modeling of the risk factors; it discriminates participants based on the natural history of the risk factor levels and, eventually, assigns all participants to groups where they have the highest probability of belonging. The plausible limitation in the trajectory method may result if the analyses produce subgroups that look like homogenous risk factor levels—however, in reality, the risk factor levels in the subgroups are more heterogenous. Hence, the method may generate groups that do not exist or oversimplify a complex reality. However, if the diagnostic criteria in the analyses are carefully followed, trajectory modeling offers an accurate method to model longitudinally measured cardiovascular risk factors and to effectively discriminate participants into clinically meaningful groups.

The potential limitation caused by reverse causation in observational studies needs to be addressed as well. In particular, the causal role of obesity in cognitive deficits and dementias has been discussed in previous literature. Importantly, the Lancet Commission acknowledged midlife obesity as a risk factor for dementia [3]. However, later life weight decline [74] and underweight [75,76] were also found to be associated with increased risk of dementia. Furthermore, later life obesity has not been shown to be associated with the risk of dementia [74]. In addition, a large-scale British study with nearly two million participants suggested that midlife obesity is not associated with the risk of dementia. However, the authors of that study argued that short follow-up (a median of 9.1 years) or missing covariates—blood pressure, serum lipids, and SES—might interrupt the observed associations. Additionally, the causal relationship between cognitive performance and elevated blood pressure [238], high total cholesterol [241,242], and obesity [245] is supported by experimental animal data.

6.6 Cardiovascular risk factor accumulation and cognitive performance

The main result of this thesis indicates that the accumulation of adverse cardiovascular risk factors—elevated systolic blood pressure, high total cholesterol, and overweight and obesity—since childhood is associated with worse cognitive performance in midlife. The cognitive tests where significant associations for cardiovascular risk factor accumulation were observed indicated poorer cognitive performance in episodic memory and associative learning, visual processing and sustained attention, and reaction and movement time. The association for risk factor accumulation was present even after age, sex, polygenic risk score, and other adulthood cardiovascular risk factors—fasting glucose, smoking, physical activity, and diet—were controlled. In the original publication II, when the observations were additionally controlled for childhood school performance, education, and childhood SES, the associations remained essentially similar.

The finding of the association between cardiovascular risk factor accumulation and worse cognitive performance is in line with the previous prospective studies conducted on adults [113,114], middle-aged [79,95,99–109,248], and old-aged [60,98] individuals. Furthermore, cross-sectional studies have observed similar associations in middle-aged populations [97,110–112]. The previous studies have observed that cardiovascular risk factor accumulation is associated with a wide range of cognitive domains, such as poorer memory [60,95,97,98,100,102–104,106–108,110,111,113,114], slower processing speed [79,99,104,107–113], worse executive function [95,97,99,103–105,107,108,112–114,248], and worse verbal abilities [100,101,104,108,110,248].

Risk factor accumulation was evaluated by calculating a cardiovascular risk score, where the trajectory groups within adverse levels in systolic blood pressure, serum total cholesterol, and BMI were considered to contribute to risk factor accumulation. Previous studies used various methods to assess risk factor accumulation, such as AHA's Life's Simple 7 ideal cardiovascular health metric [104,110–113], Framingham Risk Scores [79,99,101,103,105,106], and the CAIDE Study Risk Score [107–109]. Several other methods for assessing risk factor accumulation have also been used [95,100,102,114,248].

6.6.1 Limitations of cardiovascular risk factor accumulation studies

A significant limitation of the previous studies that assessed cardiovascular risk factor accumulation is that they used varying methods to do so. Though there are several clinical tools for assessing risk factor accumulation, it is important to note that these tools were originally developed to predict the risk of cardiovascular

disease, coronary heart disease, or stroke [91–93]. By far, the CAIDE Study Risk Score is the only tool capable of assessing midlife risk factor accumulation in relation to later life risk of dementia [90]. Previous studies used the CAIDE Study Risk Score to assess the association between midlife risk factor accumulation and cognitive performance. However, no risk factor accumulation score or tool for early life risk factor levels has been developed to assess the level of cognitive performance and later risk of cognitive deficits or even dementia, which may mainly be due to the lack of observational data on the associations since early life. The clinical tools used by previous studies to evaluate risk factor accumulation and cognitive performance might not be appropriate for early life risk factor levels. Future research is thus needed to overcome this limitation.

The cardiovascular risk factor score used in this thesis to assess cardiovascular risk factor accumulation from childhood to midlife may not be considered a clinical tool to evaluate cognitive performance later in life. Since different risk factors had different β estimates—for example, the BMI of two distinct trajectory groups were both within adverse BMI levels—it might indicate that the impact of risk factors may be unequal. Therefore, the risk score may be useful at the population level but not applicable at the individual level in clinical practice.

6.7 Serum creatinine and cognitive performance

The main results of this thesis showed that, compared to low serum creatinine, consistently higher clinically normal serum creatinine levels are associated with better short-term working memory as well as better episodic memory and associative learning in men. This association remained significant despite wide adjustments including age, childhood school performance, education, APOE genotype, antihypertensive medication use, and other adulthood cardiovascular risk factors (systolic blood pressure, total cholesterol, BMI, smoking, physical activity, diet, and diabetes and impaired fasting glucose). Similar associations, however, were not observed for women. In addition, low serum creatinine was associated with worse childhood school performance, low education, smoking, and low physical activity.

The observed association between serum creatinine and poor memory function in men has not been widely examined. Only a few previous studies have reported similar findings, but all of them used eGFR to study serum creatinine's association with cognitive performance [180,182,183] or risk of dementia [179]. Hence, no studies have directly reported observations concerning serum creatinine. Furthermore, one study used measured GFR that reflects true hyperfiltration [181], although it was conducted on the same study population as the study that also assessed the association for eGFR [180]. These studies observed that high GFR/low serum creatinine is associated with slower processing speed [180,181], worse

performance in the Six-item Screener briefly measuring recall and temporal orientation [182], and a decline in global cognition [183]. It is important to note that most of the previous studies examined the association between decreased eGFR—and thus clinically high serum creatinine, which reflects impaired kidney function—with cognitive performance. A plausible nonlinear association for serum creatinine might not thus be observed in previous studies.

In this thesis, no association between women's serum creatinine and cognitive performance was observed. There are several potential mechanisms for the lack of this association. Men and women differ in creatinine levels mainly because men have a higher muscle mass than women. Creatinine diffuses out of the cells and is excreted by the kidneys at a fairly constant rate. As more than 90% of the creatinine molecules are located in the skeletal muscle, creatinine excretion is thus estimated to be 20% less in women [249], and impaired creatinine metabolism may result in declined cognitive performance in men first. This potential mechanism might have been observed in a previous study on over two million middle-aged or old-aged South Korean participants, where increased eGFR, and thus low serum creatinine, was found to be associated with an increased risk of all-cause and vascular dementia in both sexes [179]. Interestingly, it was observed that men or individuals under 65 years with high eGFR/low serum creatinine had a higher risk of Alzheimer's disease. It can thus be hypothesized that the association between serum creatinine and cognitive performance is not yet visible in women in the Young Finns Study, where the participants are relatively young and cognitively healthy.

In this thesis, no association was observed between serum creatinine and visual processing and sustained attention or reaction and movement time. This may indicate that these cognitive domains are plausibly determined by other factors unrelated to serum creatinine. This thesis instead suggests that reaction and movement time is faster among participants with higher cumulative physical activity. Moreover, a weak association between higher physical activity and better visual processing and sustained attention was observed among men. Visual processing and sustained attention was also observed to be worse among those with consistently high systolic blood pressure, were overweight and obese since childhood, or had cardiovascular risk factor accumulated since childhood. These cognitive domains might thus be mediated via cardiovascular risk factors rather than serum creatinine. However, it can be hypothesized that, as physical activity is known to be associated with higher serum creatinine levels, it may be linked to better cognitive performance via high serum creatinine levels and other pathways.

6.7.1 Limitations of serum creatinine studies

The association between clinically normal high serum creatinine and poor cognitive performance is a somewhat novel and less-studied observation, which means that its potential mechanisms also remain uncertain, as previous literature has barely touched on the subject. Furthermore, since no experimental data exist to elucidate this observation, the plausible mechanisms can only be speculated.

In addition to cognitive performance, previous literature has proposed that high eGFR, and thus low serum creatinine, is an early manifestation of cardiovascular risk factors, such as prehypertension, hypertension, prediabetes, diabetes, obesity, and smoking. A plausible limitation of the previous studies might thus be their main focus, i.e., kidney function, because eGFR might indicate non-GFR-related factors rather than kidney function. For example, the cardiovascular risk-associated change in eGFR is suggested to be interpreted with caution because eGFR is associated with a higher number of cardiovascular risk factors compared to measured GFR [172]. Hence, high eGFR/low serum creatinine might indicate an adverse cardiovascular risk factor profile for several risk factors, possibly before they result in the clinical manifestation of any disease, and thus the accumulation of several risk factors may be linked to cognitive performance. Furthermore, serum creatinine levels are influenced by dietary protein intake and physical activity, which might be linked to cognitive performance as well.

In previous studies, impaired kidney function, which was suggested to manifest as glomerular hyperfiltration, may be a plausible mechanism for decreased eGFR/low serum creatinine. In the present study, a significant limitation is the lack of more accurate means to assess kidney function, such as measured creatinine clearance, cystatin C, or albuminuria/proteinuria levels.

Moreover, creatinine has been shown to have a role in energy metabolism in the brain and to be an end-product in the degradation of creatine and phosphocreatine [185]. Creatine and phosphocreatine degradation into creatinine in the brain is suggested to be increased in impaired brain energy metabolism in Alzheimer's disease [184,250]. Furthermore, it has been suggested that oral creatine supplementation may plausibly improve memory in healthy adults [249], which highlights the possibility that low serum creatinine levels are not potentially optimal for maintaining energy metabolism in the brain. However, the causal relations are not possible to be determined, as it remains uncertain whether better cognitive performance is caused by clinically normal high serum creatinine or clinically normal high serum creatinine is caused by better cognitive performance.

6.8 Strengths and limitations

This thesis has several important strengths. First, the Young Finns Study is a unique, large, and randomly selected population-based cohort, which enables the longitudinal examination of extensively and repeatedly measured cardiovascular risk factors from childhood to midlife with a 31-year follow-up. The study population can be thus considered representative of the general Finnish population. Second, as the study population is young and cognitively healthy, the data offers the possibility to study the associations between several risk factors and cognitive performance before the pathophysiological processes that lead to clinically detectable cognitive deficits begin. This outlook is important, as it offers potentially effective means for primary and even primordial prevention. Third, this study assessed cognitive performance using a computerized neuropsychological test battery, CANTAB®, which might reflect different cognitive domains accurately. Computerized cognitive testing might have several advantages—better precision, standardization, and reliability—compared to traditional noncomputerized tests [29,251]. Importantly, previous studies have indicated that the CANTAB® test battery may be able to predict the development of dementia in the preclinical population [252,253]. Interestingly, the CANTAB® battery might be useful to differentiate dementias, such as Alzheimer's disease and frontotemporal dementia [254]. However, it is not possible to evaluate the risk of dementia in the Young Finns Study population because it does not include participants who have dementia. Additionally, no previous large-scale observational population-based study applying CANTAB® and focusing on dementia risk exists, which prevents us from comparing our results to previous findings in populations with demented participants.

This study has some limitations that must be addressed. First, it assessed cognitive performance only once in early midlife. It is thus not possible to draw conclusions on the associations of the risk factors with the possible changes in cognitive performance. Second, high cognitive ability before age-related cognitive decline starts is shown to be important in relation to later life cognitive performance. Since the baseline cognitive performance was not assessed, this might have caused bias in the interpretation of the observational findings in the present thesis. However, childhood school performance was used as a proxy for baseline cognitive performance and a covariate in all statistical models. Importantly, the associations remained robust and significant. Third, several statistical tests were applied, which increases the probability of false-positive findings. It is important to note that the analyses in this thesis were based on strict hypotheses, and multiple testing corrections were thus not applied. Fourth, residual confounding might potentially limit interpretations in all observational studies. Some unmeasured factors might thus contribute to the observed associations with cognitive performance. However,

the statistical models were adjusted for a wide array of possible confounding factors, thus reducing the possibility of such a bias.

6.9 Future directions

Since diseases that most commonly cause cognitive deficits, such as Alzheimer's disease, might have an extremely long preclinical phase before the onset of detectable symptoms, future research on the potential risk factors that influence cognitive performance is needed [4]. Studying the associations between risk factors from childhood and cognitive performance in adulthood is thus important for life-course cognitive health promotion. To study the risk factors, it is important to note that middle-aged or old-aged populations are not necessarily optimal, as nearly 20% of individuals aged over 60 years may have at least mild deficits in cognitive performance [255]. This thesis offers novel information on risk factors, including physical activity, blood pressure, serum lipids, obesity, and risk factor accumulation since childhood as well as serum creatinine since adulthood. However, it is important that future studies confirm and replicate these observed associations.

Moreover, future studies from the Young Finns Study that focus on the other plausible risk factors from childhood that are known to influence cognitive performance in middle age or later are needed. These risk factors include glucose metabolism factors and diabetes, dietary habits, alcohol consumption, and many other behavioral and environmental factors. The future studies could also shed light on the role of childhood risk factors and risk factor profiles in old-age cognitive function and dementia risk. In addition, these studies will need to reveal whether there are any specific age windows in childhood and/or adolescence during which cardiovascular risk reduction would be of specific importance for cognitive health in adulthood. Moreover, because the studies in this thesis reported observational findings, the actual mechanisms for cardiovascular risk factors remain unclear.

While there are currently no effective pharmacologic treatments that prevent or cure the major causes of cognitive deficits, such as Alzheimer's disease, or slow its progression, several previous studies have estimated the cost savings of future interventions that either slow the clinical onset of dementia for five years or reduce the symptoms could reduce health care payments up to 40% in the US [13]. In addition to financial influences, the reduction in social burden caused by cognitive deficits would be significant. Therefore, if the associations in this thesis are causal, early interventions on potentially modifiable cardiovascular risk factors offer an opportunity for the primordial promotion of cognitive health (Figure 11) and, through that, a possibility to delay the onset of clinical cognitive deficits. The promotion of cardiovascular health already from early life and beyond is of paramount importance to improve an individual's quality of life and respond to the

increasing costs of public healthcare. This novel insight into the cardiovascular risk factors on cognitive performance is needed to direct political decision making and national health recommendations that aim to promote cognitive health across an individual's whole lifespan.

Finally, future randomized clinical trials are needed to identify the prevention potential on an individual basis [4]. In particular, multidomain cardiovascular risk factor reduction might be effective for dementia risk reduction and prevention. The recently launched World-Wide FINGERS will add much-needed knowledge on the effect of multidomain lifestyle intervention on a global scale [202].

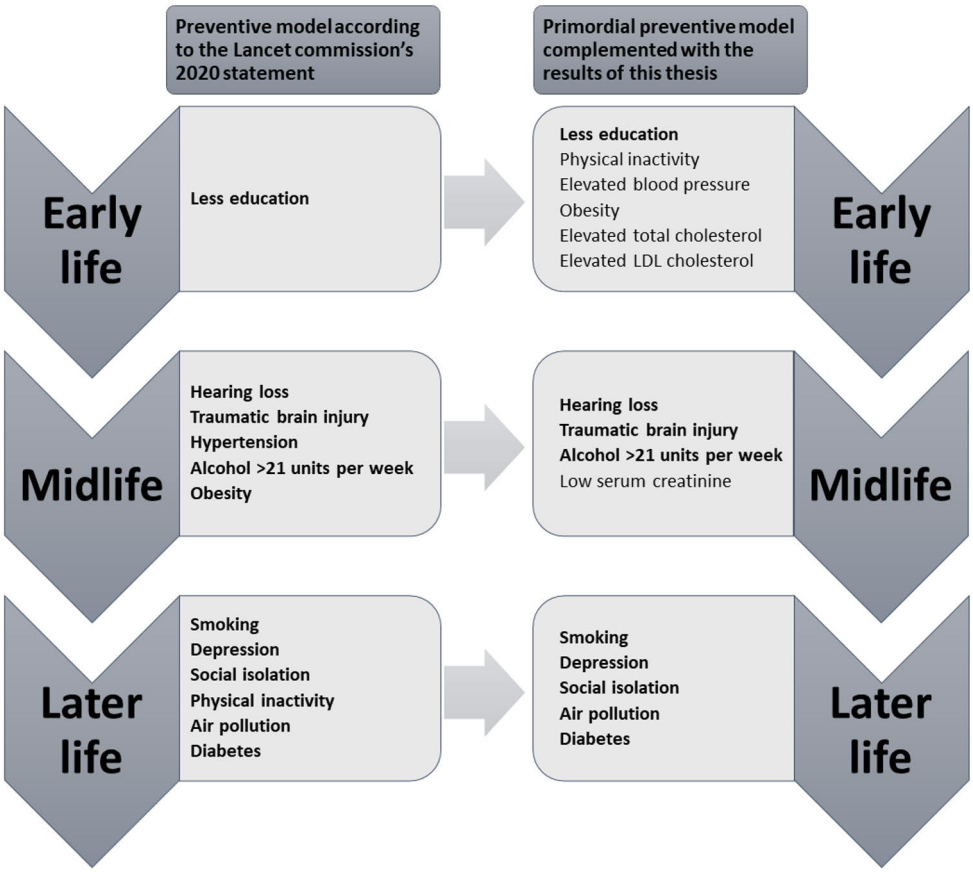

Figure 11. Potential additions to the modifiable risk factors for life-course primordial promotion of cognitive health.

7 Conclusions

As demonstrated by the studies described in this thesis, several cardiovascular risk factors already since childhood are associated with worse cognitive performance in adulthood. This highlights the importance of identifying persons with adverse cardiovascular risk factor profiles since childhood as they are those with also a higher risk of poor cognitive performance in midlife. This is important as cardiovascular risk reduction would plausibly benefit their cognitive performance.

The following are the main conclusions of this thesis:

1. Physical activity in childhood, adolescence, young adulthood, and adulthood is associated with faster reaction and movement time in midlife. Reaction and movement time was faster within all age windows and independent of the physical activity levels reported in other age windows, indicating that it is never too late to adopt a physically active lifestyle (Study I).
2. Consistently elevated systolic blood pressure and high total and LDL cholesterol since childhood are associated with poorer episodic memory and associative learning in midlife. Consistently elevated systolic blood pressure and overweight and obesity since childhood are associated with worse visual processing and sustained attention in midlife (Study II).
3. The accumulation of several cardiovascular risk factors—elevated systolic blood pressure, high total cholesterol, and overweight and obesity—since childhood is associated with poorer episodic memory and associative learning, worse visual processing and sustained attention, and slower reaction and movement time in midlife. The more the accumulation of risk factors since childhood, the worse the cognitive performance (Study II).
4. In men, high clinically normal serum creatinine in adulthood is associated with better episodic memory and associative learning as well as better short-term working memory in midlife. Serum creatinine could provide a novel and easily interpretable way to evaluate the risk of poor cognitive performance in young and healthy men (Study III).

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Juuso Olavi Hakala

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