Cardiometabolic determinants of cognitive function in later life: unravelling the roles of risk factors

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General introduction and outline of this thesis

General introduction

The worldwide increase in life expectancy has resulted in a rapid growth in the number of older people [1]. With ageing populations, the prevalence of age-related disorders such as dementia is on the rise [1]. Among patients with dementia, most are diagnosed with Alzheimer's Disease (AD). According to Central Bureau of Statistics Netherlands (CBS), the prevalence of dementia is expected to grow from 290,000 patients in 2021 to more than 500,000 in 2040 [2]. In the Netherlands, eight percent of individuals above 65 years have currently been diagnosed with dementia [1].

The clinical presentation of dementia is multifaceted. The early manifestation of dementia is known as (subclinical) cognitive impairment. Symptoms include memory loss, concentration problems, and difficulties performing daily tasks (i.e., apraxia) [3, 4]. It is important to note that subclinical cognitive impairment precedes dementia and can be detected using, for example, clinically validated cognitive screening tests such as the Mini Mental State Examination (MMSE). These screening tests are routinely used in the clinic to monitor the cognitive status of patients [5].

Currently, there is no curable treatment for dementia. The present treatment for dementia is targeted towards slowing down progression of the disease and optimizing risk factors. For example, pharmacological interventions include reducing the production of plaques composed of beta-amyloid depositions and tau-protein neurofibrillary tangles, which are neuropathological hallmarks of AD [6]. These hallmarks are correlated with neuronal degeneration, neuroinflammation, microglia activation, and overall cognitive decline [7]. However, pharmacotherapy alone cannot reverse the damage induced by these depositions and processes. Additionally, it cannot reduce the number or severity of clinical symptoms.

In addition to the development of beta-amyloid plaques and neurofibrillary tangles, the vascular component of dementia is increasingly recognized as an independent determinant of cognitive impairment [8, 9]. Vascular dementia is the second most common form of dementia, and systemic cardiovascular disease (CVD) has been identified an independent causal risk factor [9]. Moreover, dementia and CVD share many of the same risk factors, such as smoking, obesity, hypertension, depression, physical inactivity, and diabetes mellitus [8]. These risk factors often coexist in the same patients and are strongly associated with the aetiology of both diseases. Cardiac dysfunction such as heart failure, coronary artery disease and atrial fibrillation have each been associated with an increased risk of dementia [7-9]. Thus, attention is now shifting towards cardiac (dys)function and its association with the risk of cognitive impairment, as (sub)clinical vascular brain damage is becoming a key modifiable cause of dementia.

Common pathology underlying cardiovascular disease and dementia

As described, dementia and CVD share multiple (modifiable) risk factors. For example, diabetes mellitus type 2, elevated low-density lipoprotein cholesterol (LDL-C) as well as elevated triglycerides in middle-aged patients have been associated with increased 20-year cognitive decline [10, 11]. Moreover, elevated LDL-C is generally known to be a key player in the development of atherosclerotic plaques, which leads to coronary artery disease [9], and is therefore a key target for the primary and secondary prevention of CVD. However, these atherosclerotic plaques may also manifest in the carotid arteries. Research has shown that atherosclerotic plaques in the carotid arteries can lead to (sub) clinical cerebrovascular damage by altering cerebral blood flow to the brain and even cause chronic cerebral hypoperfusion, eventually exposing individuals to a higher risk of cognitive impairment [12, 13]. Moreover, a higher risk of dementia can also result from the rupture of an atherosclerotic plaque in the carotid artery, causing an ischemic stroke in brain tissue [9].

Hypertension (high blood pressure) is another overlapping risk factor associated with both CVD and dementia. Research has shown that hypertension in mid-life increases the risk of dementia in later life [14]. A recent meta-analysis of 27 imaging studies found that increased 24-hour blood pressure variability was associated with an increased burden of white matter hyperintensities in the brain and small-vessel disease [15]. Hypertension has been established as the most prevalent vascular risk-factor that accelerates cognitive aging, and although modifiable, successful blood pressure control does not mitigate the risk of cognitive dysfunction [16].

Treatment of elevated LDL-C, triglycerides and hypertension are currently included in the management of CVD, as this significantly reduces the risk of coronary artery disease, atherosclerotic plaques and cerebrovascular events [9, 16]. Interestingly, the improved management of CVD has also become a key contributor to the decrease in dementia incidence, even though the prevalence of dementia is on the rise [17-19]. To illustrate, population-based cohort studies have shown a decrease in dementia incidence and partially attributed this trend to an increased use of antidiabetic, lipid-lowering and antithrombotic medication [17-19]. Thus, the reduction in vascular risk factors at population level will continue to affect the incidence of dementia despite the growing number of older individuals.

Missing links

Optimizing risk factors remains the key disease-modifying intervention in dementia, as the disease is currently incurable, and clinical symptoms seem to be irreversible. Therefore, further examining pathways underlying the relationship between cardiovascular disease and dementia can improve our understanding of the pathophysiology and potentially lead to improved management of overlapping risk factors. Although numerous components of cardiovascular disease such as hypertension and elevated LDL-C have been extensively

studied in relation to dementia, various risk factors remain to be unravelled. Therefore, the aim of the present thesis is to examine the pathways between different risk factors linking cardiovascular disease to cognitive function, using data from an older population at increased risk of cardiovascular disease. We hypothesize that changes in physiological functioning caused by (sub)clinical cardiovascular disease are possible mediators in cognitive dysfunction. These changes in the physiological functioning are, amongst others, blood serum metabolite concentrations, weight loss or even variation in length of ventricular depolarization. In other words, we aim to investigate whether novel risk factors associated with cardiovascular disease are also risk factors for cognitive decline.

Observation versus causality

It is important to note that the cardiometabolic determinants used in the present thesis are *risk factors*, which are different from *risk markers*. Risk factors *can* be causal to a disease and modification *can* affect disease risk [20]. Risk markers, on the other hand, implicate the definitive *absence* of a causal relationship, meaning modification of a risk marker will not change the risk of a disease [20]. In the present thesis, we aim to first unravel cardiometabolic risk factors using multivariable-adjusted observational studies, before evaluating whether risk factors can potentially be interpreted as causal with further exploration.

A statistical method that has been increasingly popular in recent years to infer causal associations is Mendelian Randomization (MR). MR can be used to evaluate causality between exposures and outcomes, using genetic variations as instrumental variables. Single-nucleotide polymorphisms (SNPs) are commonly the genetic instruments used in MR, which are identified using Genome-Wide Association Studies (GWAS) often performed in large populations. Several assumptions must be met in order to perform an MR study [21]. First, the genetic variants must be associated with the exposure. This can be ensured by performing a GWAS on the exposure. Second, the genetic variants are associated with the outcome exclusively through the exposure. Last, genetic variants are independent of confounders. In this way, MR analysis is able to overcome the limitations of other epidemiological studies such as confounding and reverse causation [21]. Although randomized controlled trials (RCTs) are commonly the gold standard to assess whether observational associations are also causal, they often require long follow-up times, large sample sizes and are costly, and thus MR may provide an alternative to help identify relevant risk factors, especially when there is a lack of intervention tools. However, it is important to emphasize that the current MR studies are limited by the use of only a single cross-sectional assessment of a specific risk factor as exposure reflective of a long-life exposure to a higher of lower risk, and that specific markers have been underpowered to be examined till recently. For this reason, multivariable-adjusted observational studies embedded in well-characterized cohorts still add to the scientific field.

Outline of this thesis

Part 1: Cardiovascular determinants of cognitive function

The electrocardiogram (ECG) is used for diagnosis and prognosis of CVD [22]. Previous studies have found ECG-based measurements such as increased heart-rate variability, wider QRS-T angle, and left-ventricular hypertrophy to be associated with worse cognitive test performance [23, 24]. In **Chapter 2,** the association between ECG-based intervals, cognitive function, and MRI-based brain parameters are explored at baseline and during follow-up in a cohort of older adults at increased risk for cardiovascular disease.

Animal studies have found troponin gene expression in the brain [25-27]. Clinical studies have measured higher serum troponin and severe white matter lesions in patients following stroke, suggesting troponin may be present in cerebral vasculature and play a role in cognitive changes [25-28]. In **Chapter 3,** the association between cardiac troponin, cognitive function, and dementia are examined by means of a systematic review.

Results from epidemiological studies imply a connection between markers of cardiac (dys)function such as troponin I and T, N-terminal pro B-type natriuretic peptide (NT-proBNP) and growth-differentiation factor 15 (GDF15), and risk of dementia and poorer cognitive performance [29-31]. However, causal inferences cannot be made from regression-based prospective cohort studies, and therefore MR analysis is a more appropriate method to investigate causality. In **Chapter 4**, causality of cardiac blood biomarkers such as troponin in dementia and cognitive performance is investigated using MR.

Part 2: Metabolic determinants of cognitive function

High amounts of white adipose tissue (WAT), as seen in (abdominally) obese individuals, can lead to excess leptin secretion and leptin resistance, both of which have been found in association to cognitive function and Alzheimer's disease [32, 33]. However, the question that remains is whether the association between obesity and cognitive function is dependent on leptin. Therefore, in **Chapter 5,** the interplay of circulating serum leptin and obesity are investigated in relation to cognitive function and MRI-based cerebral volumes in older adults.

Unintentional weight loss and variation in body weight in older adults are associated with increased frailty and functional decline [34, 35]. In addition, other markers of unstable homeostasis such as high variability in blood pressure and low-density lipoprotein cholesterol (LDL-C), have also previously been associated with worse cognitive function [36, 37]. In **Chapter 6,** loss of body weight and body weight variability during 2.5-years of follow-up are examined in relation to cognitive function and activities of daily living.

Metabolomics is the study of serum blood metabolites, and various metabolites have been linked to the pathophysiology of diseases such as diabetes, CVD, and dementia. Recently, a score (the MetaboHealth score) was developed to predict all-cause mortality and specific disease-related mortality using 14 metabolites from 12 cohort studies (44,168 individuals) [38]. In **Chapter 7,** the role of metabolomics in cognitive function is examined. Our aim is to evaluate in which way the MetaboHealth score associates with cognitive and daily functioning, and cognitive and functional decline.

Finally, **Chapter 8** summarizes the results of this thesis and discusses future implications.

Description of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)

Study population

To investigate the research questions, we used data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study. The PROSPER study was a large prospective multicentre RCT which assessed the safety and efficacy of pravastatin [39]. Older adults aged 70-82 years from the Netherlands, Scotland, and Ireland were enrolled in the study if they had pre-existing vascular disease or increased risk of vascular disease due to diabetes, smoking, or hypertension. Pre-existing vascular disease included either physician-diagnosed stable angina, intermittent claudication, or one of the following >6 months prior to study entry: stroke, transient ischemic attack, myocardial infarction, arterial surgery, or amputation for vascular disease [39]. Exclusion criteria, especially relevant to the present thesis, include poor cognitive function at baseline (Mini Mental State Examination (MMSE) <24 out of 30 points). More details regarding inclusion and exclusion criteria have been described elsewhere [39].

A total of 5,804 men and women entered the study and were randomly assigned 40 mg pravastatin per day or a placebo for an average 3.5-year intervention period. The primary outcome measure was the occurrence of major vascular events, in light of secondary prevention. This includes the combined endpoint of coronary heart disease death (definite/suspect), myocardial infarction (definite/suspect), and stroke (definite/suspect). In the present thesis, participants from both intervention and control groups were included in the analyses as pravastatin does not affect cognitive function [40].

Cognitive function tests used in PROSPER

The MMSE was measured at baseline, where a score >24 out of 30 points served as an inclusion criterion. However, the MMSE is not sensitive enough to detect cognitive changes during a short follow-up time, especially in participants with normal cognitive functioning at baseline, and contains a ceiling effect; many participants consistently perform at a near maximum level [41]. Therefore, a special test battery for cognitive function was developed to test fluid abilities in PROSPER participants. Fluid abilities are areas of cognitive functioning that tend to change with time or in response to medical interventions. PROSPER tested the following fluid abilities: memory, attention, and general cognitive speed [41]. Due to the multicentre nature of the study, cognitive tests used pictures, colours, and digits rather than words to prevent language or cultural differences.

Selective attention was examined using the Stroop-Colour-Word-Test (Stroop). The Stroop test consists of three parts, each with 40 stimuli. The participant was asked to read or name as quickly as possible: (1) colour names, (2) coloured patches, and (3) colour names printed in incongruously coloured ink; for example, “blue” printed in red letters, where the participant had to say “red” [41]. This is also known as cognitive interference; the ability to disregard irrelevant information. The number of seconds needed to complete the third task served as the main outcome parameter [41].

Processing speed was tested using the Letter-Digit-Coding test, a modified version of the Symbol-Digits Modalities test [41]. Participants had to fill in symbols near letters as fast as possible, according to a key presented at the top of the test sheet. The total number of correct entries out of 125 letters within 60 seconds served as the outcome measure, where an older adult typically makes 15-30 correct entries, avoiding ceiling effects [41].

Memory was tested using the Picture-Word Learning test, an adaption of the Groningen-Fifteen-Words-Test. Study participants were shown fifteen pictures successively, with two seconds per picture, and afterwards were asked to recall as many pictures as possible [41]. This process was repeated three times, and delayed recall was tested after 20 minutes. The number of correct recalled pictures over the three repetitions served as the outcome for the "immediate" version of the test, and the number of correct recalled pictures after 20 minutes served as the outcome for the "delayed" version of the test [41].

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