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

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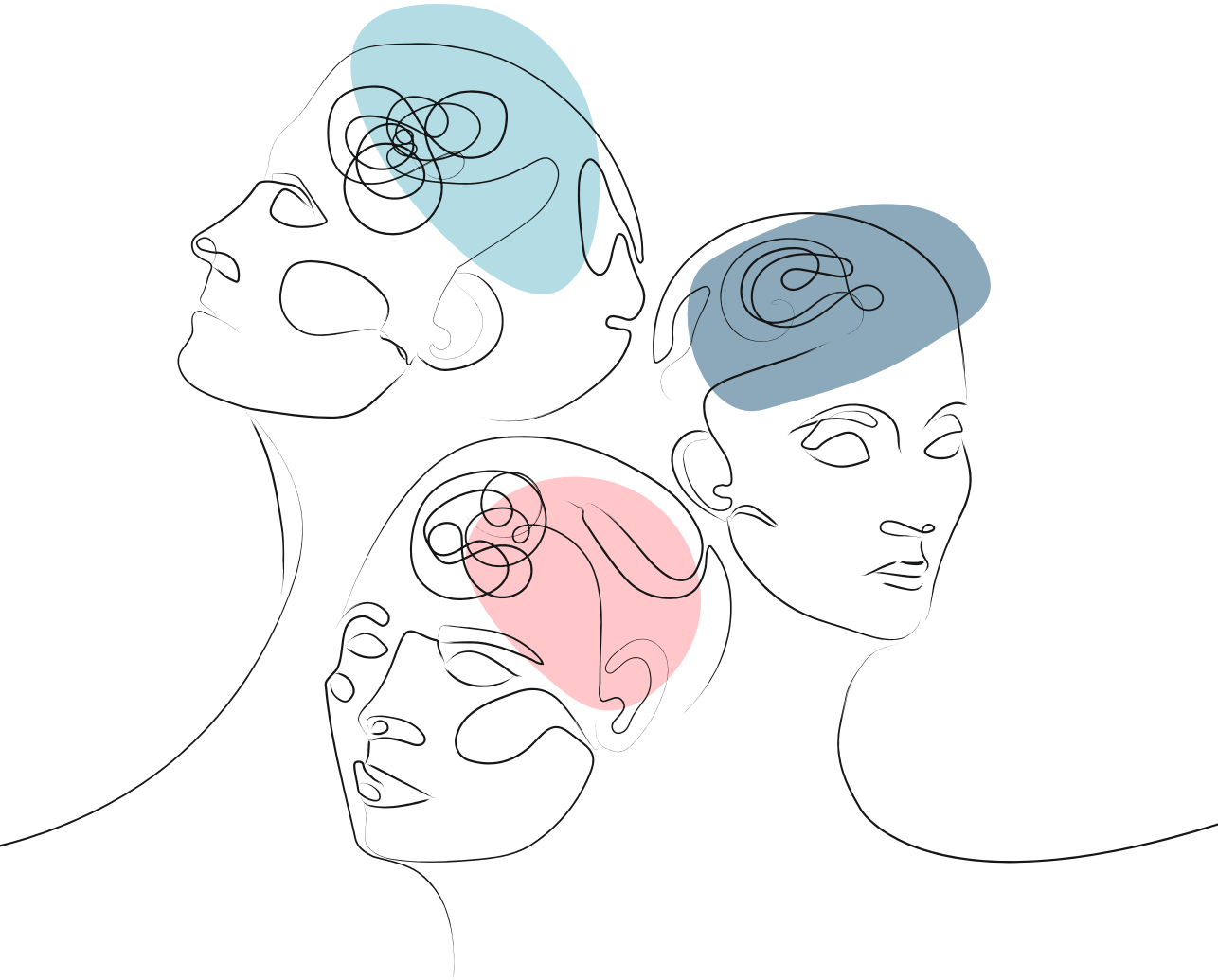

9

English summary
Nederlandse samenvatting
List of publications
Dankwoord
Curriculum vitae

English summary

Introduction

The prevalence of dementia is increasing due to the growing number of older people. As there is no effective cure, current interventions target slowing down progression of the disease and optimizing risk factors. Many risk factors that have been associated with dementia, like diabetes mellitus type 2, smoking and obesity, are also associated with cardiovascular disease (CVD). In addition, specific types of CVD such as heart failure, coronary artery disease and hypertension are associated with an increased risk of dementia. Examining the relationship between CVD and cognitive dysfunction (a preclinical stage of dementia) may lead to improved understanding of the pathophysiology. Although multiple components of CVD have already been extensively studied in relation to dementia, there are still many risk factors for which additional evidence is required to understand the mechanisms underlying the association between CVD and dementia.

Aim of this thesis

The aim of this thesis is to examine the pathways between different cardiometabolic risk factors and cognitive function, using data largely derived from an older population at increased risk of CVD. We hypothesize that changes in physiological functioning caused by (sub)clinical CVD are possible mediators within the pathway leading to cognitive dysfunction.

Summary of key findings

This thesis is divided into two parts. The first part of the thesis describes cardiovascular risk factors in relation to cognitive dysfunction in a population of older adults at higher risk of CVD. The electrocardiogram (ECG) is an affordable, easily available diagnostic tool used to measure cardiac function. In **Chapter 2**, we investigated various ECG-based intervals in relation to cognitive function. We found that a longer JT-interval, reflecting longer ventricular repolarization, was associated with worse general cognitive function at baseline. Although our study population was at a higher risk of or already had an established history of CVD, they were free of dementia at baseline. This means that subclinical changes in cardiac function may exist before cognitive dysfunction becomes apparent. Troponin, a biomarker of cardiac myocyte (muscle cell) damage, has also been associated with accelerated cognitive decline and increased risk of dementia. In **Chapter 3**, we performed a systematic review of published cohort studies investigating the association between troponin concentration in the blood, cognitive function and/or dementia. The twelve cohort studies that were included reported that higher cardiac troponin levels are associated with higher risk of cognitive impairment, but not with an increased risk of either incident dementia or with incident Alzheimer's Disease. Thus, troponin may be a risk marker of future cognitive dysfunction. In line with these findings, we wanted to explore whether troponin-T and troponin-I and other markers of cardiac function (N-terminal pro B-type natriuretic peptide (NT-proBNP) and grow-differentiation factor 15 (GDF15)) may be causally associated with dementia in **Chapter 4**. As we cannot infer causal associations from regression-based analyses embedded in

observational cohort studies, we used Mendelian Randomization (MR) analysis. MR analysis uses genetic variations as instrumental variables and as a result these are less harmed by most confounding and reverse causation. This enabled studying the associations of genetically-influenced higher serum cardiac biomarkers in relation to dementia. However, we did not find evidence for possible causal associations between cardiac biomarkers, cognitive function and dementia. These results suggest that the underlying pathways between CVD and cognitive changes are more likely to employ other mechanisms than biomarkers of cardiac (dys)function.

The second part of this thesis describes metabolic risk factors in relation to cognitive function. Obesity, defined as a body mass index (BMI) above 30 kg/m^2, is a modifiable risk factor for several adverse health outcomes. However, the pathways in which body composition can affect the brain are not well understood. We aimed to investigate the association of BMI and circulating leptin with MRI-based brain volumes and cognitive function in a cohort of older adults in **Chapter 5**. More specifically, we aimed to investigate the independent associations of BMI and circulating leptin. Leptin, a hormone signaling satiety, is secreted by adipose tissue, which is the largest endocrine organ in the human body. We found that a BMI above 30 kg/m^2, independent of leptin, was associated with worse cognitive function and higher volumes of the amygdala and the hippocampus. Thus, our results suggest that leptin is not a mediator between BMI and cognitive function, implying distinct biological mechanisms. In addition to BMI, we were also interested in other measurements of body weight like loss of weight and body weight variability. In **Chapter 6**, we found that older adults with ≥5% loss of baseline body weight and higher weight variability scored significantly lower in four domains of cognitive function during 2.5-years of follow-up, compared to adults who maintained either a stable body weight or gained weight. Thus, weight loss and higher weight variability may signify an early manifestation of cognitive decline. Next to measurements of body composition, we also studied the role of metabolomics (the analysis of small blood serum metabolites) in light of cognitive impairment in older adults. Metabolites are small molecules, intermediate or end products of metabolism, such as fatty acids or amino acids. We included metabolomics in our analyses in the form of a composite score of 14 different metabolites. We assessed the association between the metabolomics-based score with cognitive function and functional independence in **Chapter 7**. We found that a higher metabolomics-based score was associated with worse cognitive function and higher functional dependence. Thus, metabolite-based scores may also be used to identify individuals at a higher risk of future cognitive decline.

Discussion

The results described in this thesis contribute to the knowledge on potential constituent pathways leading to cognitive impairment, which is the phase preceding the clinical manifestation of dementia. We found that various cardiometabolic risk factors, such as prolonged ventricular repolarization, higher troponin (although not causal), higher BMI, loss of body weight and a higher metabolomics-based score were associated with worse

cognitive function. Thus, tackling these risk factors in addition to treatment of established CVD may be of benefit to future cognitive changes.

Although research shows that there is an increase in the number of older adults and the prevalence of dementia, the incidence of dementia is in fact decreasing. This is partially due to the improved prevention of CVD, in line with the findings of this thesis, as we established that various cardiometabolic risk factors are associated with worse cognitive function. Thus, future research should examine whether long-term treatment of CVD, such as treatment of hypertension, can actually prevent cognitive decline. The results of this thesis highlight different cardiometabolic pathways that may lead to cognitive decline and calls for further research into optimizing cardiometabolic health in order to reduce the risk of dementia.