CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
THE RELATIONSHIP OF DEMENTIA WITH VASCULAR FACTORS

Due to the aging of the population, the number of incident cases of dementia is expected to increase significantly.\textsuperscript{1,2} In 2015, the number of individuals suffering from dementia worldwide was estimated at 46 million and is projected to reach nearly 132 million in 2050.\textsuperscript{1} Because of its associated cognitive and functional impairments, dementia is one of the major causes of disability and dependency among older individuals worldwide.\textsuperscript{3} Not only does dementia cause serious distress for patients and their caregivers, it also leads to dramatic economic burdens and has a devastating impact on health care resources.\textsuperscript{2,4} Alzheimer’s disease, pathologically characterized by the presence of plaques containing the beta amyloid protein and tangles containing the hyperphosphorylated tau-protein,\textsuperscript{5} is currently the most common form of dementia, followed by vascular dementia as the second most common type.\textsuperscript{6} Together these diseases are estimated to contribute to up to 80% of all cases worldwide.\textsuperscript{6} While in the past a strict distinction was made between Alzheimer’s disease and vascular dementia, more recent insights suggest that the borders between both conditions are not as clear and that mixed pathologies are common, especially in older dementia patients (over 80 years).\textsuperscript{7-9} Clinico-pathologic research has revealed that a majority of patients who are clinically diagnosed with Alzheimer’s disease actually have multiple cerebral pathologies, including significant cerebrovascular pathology, and only a minority of patients suffers from pure neurodegenerative Alzheimer’s disease.\textsuperscript{9-11} During life, the coexisting vascular changes may contribute in a synergistic way to cognitive impairment by lowering the burden of plaque and tangle load that is needed to give rise to cognitive decline.\textsuperscript{12} Neuroimaging studies have shown that cerebrovascular lesions, including white matter lesions and (silent) cerebral infarctions, are often present in patients clinically diagnosed with Alzheimer’s disease\textsuperscript{13} and that presence of these lesions in older individuals without dementia increases the risk of developing Alzheimer’s disease in the future.\textsuperscript{14,15} Furthermore, observational studies have found associations between cardiovascular risk factors including hypertension, diabetes mellitus, smoking, obesity, and physical inactivity with an increased risk of developing dementia and in particular Alzheimer’s disease.\textsuperscript{16-23} It has been estimated that up to a third of all Alzheimer’s disease cases worldwide can be attributed to these potentially modifiable risk factors, together with depression and low educational attainment.\textsuperscript{24} Given that until now no cure or treatment to slow down the disease process has been found for dementia, developing strategies to prevent dementia is paramount. The vascular component in the pathogenesis of Alzheimer’s disease (and dementia in general) could be an important target. However, previous single-domain prevention trials targeting vascular risk factors have yielded inconsistent results.\textsuperscript{25,26} Multidomain prevention trials targeting several risk factors concurrently could offer a better opportunity to study the effects on cognition and dementia, but are rela-
tively sparse in older individuals. The Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study, a randomised-controlled trial (RCT) of multi-component cardiovascular treatment in older individuals with vascular disease, did not find any clinical benefits on cognitive outcome. In contrast, an RCT of an 18-month multidomain lifestyle intervention in a group of Korean community-dwelling older individuals showed higher cognitive function as measured with the Mini-Mental State Examination in the intervention group. The Mental Activity and eXercise (MAX) trial that assessed the combined effects of physical plus mental activity on cognitive function in inactive older adults with cognitive complaints reported an improvement in global cognitive function after three months follow-up, but without differences between intervention and control groups. More recently, results of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), an RCT of a 2-year multidomain intervention aimed at modifiable vascular and lifestyle-related risk factors, indicated a small improvement on a composite score of tests for cognitive functioning among older individuals with an elevated dementia risk score. Whether such an intervention can actually prevent dementia on the longer term is however still unknown. The Prevention of Dementia by Intensive Vascular Care (preDIVA) trial was designed to test this hypothesis.

**THE PREVENTION OF DEMENTIA BY INTENSIVE VASCULAR CARE TRIAL**

The preDIVA trial was an open cluster-randomised controlled trial carried out in primary care, designed to evaluate whether a multidomain intervention targeting vascular and life-style related risk factors can prevent or postpone dementia and all-cause disability in community-dwelling older persons (Figure 1). All eligible individuals aged 70-78 years from participating general practices were invited to take part in the study. The only exclusion criteria were a diagnosis of dementia and any condition that was assumed to impede a successful long-term follow-up (e.g. metastatic malignancy, alcoholism). Between June 2006 and March 2009, 3526 individuals were randomised after a baseline assessment to receive intensive vascular care or standard care. The intervention consisted of four-monthly visits to a practice nurse who addressed the cardiovascular risk profile of the individual participant and provided lifestyle advice. If necessary, medical treatment for cardiovascular risk factors was initiated or optimised according to Dutch general practice guidelines. Individuals in the control group received care as usual. Follow-up measurements were performed every two years with a total follow-up of six to eight years. The study was prolonged up to eight years for individuals who were randomised early into the trial to allow these participants to continue until the final assessments of the last participants were completed. The preDIVA trial was characterized...
by a pragmatic design with a relatively long period of follow-up and was the first trial to evaluate the effect of intensive vascular care with dementia as primary outcome, rather than cognitive performance or decline which have mainly been used in previous trials. Secondary outcomes were all-cause mortality, cardiovascular events, cognitive decline, and depression. The final follow-up visits were completed in March 2015.

![Flow-chart of the preDIVA study](image)

**Figure 1. Flow-chart of the preDIVA study**

### THE RELATIONSHIP OF SYMPTOMS OF APATHY AND DEPRESSION WITH VASCULAR FACTORS

In addition to dementia, late-life depression is an important public health problem in older individuals leading to substantial reductions in quality of life.\(^{32-34}\) Up to 4% of community-dwelling older persons aged 65 years and older suffer from major depression and clinically significant depressive symptoms occur in approximately 8 to 16% of these individuals.\(^{33}\) Depression, just as dementia, has frequently been associated with cardiovascular risk factors and disease.\(^{35}\) In 1997, the "vascular depression" hypothesis was coined by Alexopoulos and proposes a vascular contribution to the aetiology of late-life depression.\(^{36}\) This hypothesis was mainly based upon a high comorbidity of depression,
vascular disease and cardiovascular risk factors, the frequent occurrence of depression after stroke, and the high prevalence of white matter lesions in individuals with late-onset depression. However, one year later, in 1998, Fones argued that the clinical profile described in vascular depression, with pronounced cognitive deficits and psychomotor retardation in the absence of low mood and with limited depressive cognitions, could probably be better classified as apathy. He underlined that, although differential diagnosis between both conditions is often difficult, apathy should be considered as a condition that is clinically and conceptually distinct from depression and that differentiation of both conditions could be of importance from a treatment perspective.

Apathy, which is primarily defined as a disorder of motivation, can indeed occur in the context of depression, but can also occur independently, without symptoms of guilt, helplessness, hopelessness, and a negative mood. It is observed in individuals with neurodegenerative diseases, such as dementia and Parkinson's disease, as well as in older individuals from the general population. In line with the notion of Fones, van der Mast et al. hypothesized that, in old age, vascular disease would predispose for apathy rather than depression. In a cohort of 500 community-dwelling persons over the age of 85, they observed that presence of vascular pathologies was associated with apathy and that a history of vascular disease increased the risk of developing apathy, but not depression. Based on these findings, van der Mast et al. introduced the “vascular apathy” hypothesis. Consistent with this hypothesis, Sugawara et al. found that a lower ankle brachial pressure index, as a measure of atherosclerosis, was an independent predictor of apathy, but not depression in a community-dwelling population. Further corroborating the vascular apathy hypothesis, we observed an association of apathy symptoms with a history of cardiovascular disease and stroke and with several cardiovascular risk factors in community-dwelling older individuals. All these findings together might suggest a role of vascular factors in the aetiology of apathy. If apathy symptoms are indeed a marker of underlying vascular disease, it is conceivable that presence of these symptoms is also predictive of future cardiovascular disease and stroke. Furthermore, given the lack of self-motivation and diminished goal-directed behaviour, apathy symptoms may increase the risk of new vascular events by inducing unhealthy behaviours, such as physical inactivity, and other cardiovascular risk factors. This could be of importance for identifying potential targets for cardiovascular disease prevention.
THE RELATIONSHIP OF SYMPTOMS OF APATHY AND DEPRESSION WITH INFLAMMATION

A substantial body of literature has been published over the last decades suggesting that inflammation plays an important role in the pathophysiology of depression and depressive symptoms. Multiple inflammatory markers have been recognized as potentially significant, including cytokines, chemokines, and acute phase reactant proteins. In this research, C-reactive protein, one of the acute phase reactant proteins, has received substantial attention. Findings of meta-analyses indicate that elevated levels of C-reactive protein are associated with both present and future depression. Although the exact pathophysiological mechanisms underlying the association between inflammation and depression are as yet unknown, one line of evidence suggests that, in old age, depression may occur as a consequence of a low-grade inflammatory reaction that is triggered by underlying vascular disease. In this view, depression has also been compared to sickness-behaviour, which can be seen as a behavioural response to systemic inflammation, leading to symptoms such as somnolence, loss of energy, malaise, and diminished interest in activities. However, this cluster of symptoms appears to overlap with symptoms of apathy and, given that apathy and depression may be confused due to corresponding clinical features, it is conceivable that part of the association between inflammation and depression may actually be driven by apathy symptoms. In line with this, particularly somatic symptoms of depression, such as loss of energy and psychomotor retardation, and atypical depression have been associated with several inflammatory markers. The relationship between inflammation and apathy has been addressed in only a few studies and conflicting results were observed. In two studies in older individuals with cognitive impairment an association was found between apathy and markers of inflammation, whilst no such association was observed in a community-sample of the oldest old. Whether inflammation is associated with apathy in younger older individuals without apparent cognitive impairment remains to be elucidated.

OUTLINE OF THIS THESIS

This thesis is divided in two parts. Part I consists of chapter 2 and discusses the results of the preDIVA study in which the effect of multidomain intensive vascular care on the prevention or postponement of dementia was evaluated in 3526 community-dwelling older individuals. The main objective of Part II of this thesis was to assess whether symptoms of apathy and depression are differentially associated with future vascular disease in community-dwelling older individuals and to evaluate potential mechanisms
underlying these relationships. In chapter 3, we assessed the association of apathy and depressive symptoms with future cardiovascular disease and stroke using the two-year follow-up data of individuals without previous vascular disease from the preDIVA study. In this same population, in chapter 4 we evaluated whether apathy and depressive symptoms are differentially associated with several well-established cardiovascular risk factors and whether these risk factors act as mediators in the relationships of apathy and depressive symptoms with future cardiovascular disease. Structural equation modelling was used to quantify both the mediating role of cardiovascular risk factors in these relationships and the unique contribution of both apathy and depressive symptoms to future cardiovascular disease over and above what cardiovascular risk factors explain. In chapter 5, using data from the preDIVA study population, we assessed whether increased levels of C-reactive protein, as a systemic marker of low-grade inflammation, are differentially associated with present and future apathy and depressive symptoms. Chapter 6 reports the results of a large-scale meta-analysis of individual participant data that aimed to externally validate the findings regarding the association of apathy and depressive symptoms with future cardiovascular disease as described in chapter 3 and to assess the association of these symptoms with mortality. For this purpose, we set up the Initiative on CArdiovascular disease Risk and Apathy (ICARA), an international collaboration of 21 longitudinal population-based studies to share and pool data. Chapter 7 of this thesis provides a general discussion of the main findings of this thesis, including potential clinical implications and directions for future research, and an overall summary is given in chapter 8.
REFERENCES


