Chapter 1

General introduction
Chapter 1

General introduction
Alzheimer’s disease and vascular dementia are progressive irreversible brain disorders that result in memory loss, personality changes and unusual behaviour. Increased life expectancy in developed countries is expected to lead to a dramatic rise in the number of subjects with Alzheimer’s disease and vascular dementia. One out of four 85-year-old subjects suffers from dementia. Since no effective cure for dementia is currently present the majority of these subjects will need long-term care.

The accepted view in the field of dementia is that Alzheimer’s disease and vascular dementia develop from different aetiologies. It has been suggested that amyloid-beta plays a crucial role in the development of Alzheimer’s disease, whereas cerebrovascular disease leads to vascular dementia. Definitions of these two disorders should be firm, and the criteria to make a clinical diagnosis of either Alzheimer’s disease or vascular dementia should be independent of each other. In the current situation, however, the clinical diagnoses of Alzheimer’s disease and vascular dementia are not independent of each other. Since the clinical diagnoses of Alzheimer’s disease and vascular dementia are linked by the presence or absence of cerebrovascular disease they are intertwined. The presence of cerebrovascular disease has to be excluded before the clinical diagnosis of Alzheimer’s disease can be made, whereas the clinical diagnosis of vascular dementia can only be made when the deterioration in cognitive functioning is accompanied by cerebrovascular disease.

Theoretically the dividing line between Alzheimer’s disease and vascular dementia, based on the presence or absence of cerebrovascular disease, does not pose a problem. In the clinical situation, however, it is difficult to determine whether cerebrovascular features, which are frequently detected on imaging, cause dementia. The widespread use of MRI shows that at least 30% of all elderly people have silent cerebral infarctions. However, it is not clear whether these silent infarctions have contributed to cognitive impairment or dementia. The findings from the examination of the brains of subjects diagnosed with Alzheimer’s disease and the brains of subjects without dementia throw further doubt on the current criteria to diagnose either Alzheimer’s disease or vascular dementia. By contrast with the brains of subjects without dementia the brains of subjects with both clinically diagnosed and autopsy-proven Alzheimer’s disease often show more multiple vascular lesions. At the same time, the brains of subjects clinically diagnosed with vascular dementia show pathological changes, i.e. amyloid plaques and tau pathology, which are considered to be characteristic of Alzheimer’s disease. Finally, amyloid plaques and tau pathology are often found in the brains of elderly people who did not suffer from dementia.

The post-mortem correlates suggest that the various pathologies of the late-onset type of dementia, both vascular dementia and Alzheimer’s disease, are not mutually exclusive. A unifying hypothesis is that atherosclerotic disease causes clinical and subclinical ischaemic diseases in the brain, which contribute to the development of late-onset dementia. Such a multicausal interpretation of the observational data provides an explanation for the findings that in old age treatment of cardiovascular risk factors, such as high serum cholesterol and hypertension, is associated with a decreased risk of vascular dementia as well as Alzheimer’s disease.
The post-mortem findings which suggest that the differences between vascular dementia and Alzheimer’s disease are not distinct question whether the currently used definitions of Alzheimer’s disease and vascular dementia are correct. It is tempting to speculate and redefine late-onset type of dementia, by using criteria irrespective of a possible cause of cognitive decline. Several studies recognise that there is a transition between the extremes of “optimal” cognitive functioning and dementia 13,14. These studies, based on the “brain reserve capacity theory”, assume that there is a continuum in cognitive functioning. This means that some subjects, i.e. those with less brain reserve capacity, are more likely to surpass the threshold beyond which the presence of dementia becomes clinically apparent15,16. The advantage of regarding cognitive functioning as a continuum is that it can be described irrespective of a possible cause of poor cognitive functioning. The clinical classification of dementia, on the contrary, is dependent on criteria such as the presence or absence of cerebrovascular disease, or the presence or absence of amyloid plaques. It is therefore interesting to investigate risk factors contributing to “poor” cognitive functioning, i.e. cognitive impairment, in the general population irrespective of the presence of Alzheimer’s disease or vascular dementia. This can be done by using sophisticated neuropsychological tests, which only measure cognitive functioning.

In this thesis the effect of vascular determinants on cognitive functioning will be studied. The focus in this chapter will be on the already known effects on cognitive functioning of “classical” vascular risk factors, such as gender, diabetes, hypertension and high serum cholesterol, and a more recently identified risk factor, that is inflammation.

**Gender**

Several studies show that the prevalence of dementia and poor cognitive function is higher in women than in men. A high level of education is associated with a higher socio-economic status and reduced mortality. A high level of education is also associated with a lower prevalence of dementia and less cognitive impairment 15,16. Since in general elderly women have received less formal education than men it has been suggested that a high level of education is a plausible explanation for the finding that the prevalence of dementia and poor cognitive function is higher in women than in men. Another possible explanation for the difference in cognitive functioning between women and men is that post-menopausal oestrogen deficiency leads to cognitive impairment in women. Several studies describe a beneficial effect of oestrogen replacement therapy on cognitive function 17,18. However, in all observational studies the comparisons suffer from selection on health and it is yet unclear which part of the beneficial effect is real 19. The ultimate proof lies within randomised-controlled trials of post-menopausal hormonal replacement therapy investigating the effects on cognitive functioning. However, the findings of these trials are conflicting since the hormonal replacement therapy is associated with both a beneficial effect20 and no effect on cognitive function in subjects with dementia 21,22.

**Type-2 diabetes**

Both cross-sectional and longitudinal studies show that diabetes is associated with dementia or cognitive impairment 23-25. There are several mechanisms that can explain this finding. Evidently, clinical stroke,
which is more present in subjects with diabetes\textsuperscript{26,27} is associated with a poor cognitive function and dementia\textsuperscript{9}. This is not the only plausible explanation. Advanced glycation end products in the brain could also explain the increase in poor cognitive functioning and dementia\textsuperscript{28,29}, since pathological changes in the glucose metabolism lead to an increase in advanced glycation end products. These irreversible, protease-resistant, cross-linking proteins are formed by a non-enzymatic reaction between glucose and protein amino groups. Several studies suggest that these advanced glycation end products lead to an increased deposit of amyloid-beta in the brain, which subsequently could lead to a poor cognitive function and dementia\textsuperscript{28,29}. Finally, experimental animal studies show that hyperglycaemia leads to a reduced endoneurial blood flow resulting in endoneurial hypoxia and nerve conduction deficits\textsuperscript{30}.

**Hypertension**

The finding that treatment of isolated systolic hypertension in elderly subjects reduces the incidence of dementia by 50\% emphasises the contribution of hypertension to the development of dementia and cognitive impairment\textsuperscript{12}. Longitudinal studies have shown that both systolic and diastolic blood pressure had increased 10 to 15 years before the onset of dementia\textsuperscript{31,32}. These observational studies have also shown a decline in blood pressure level in the years before dementia becomes clinical apparent. Blood pressure levels were then similar or lower than those in non-demented individuals. Over a long period of time these findings suggest that hypertension increases the risk of dementia. Since hypertension leads to stroke and subclinical ischaemic events in the brain, which are associated with dementia, it is a very plausible determinent of the development of dementia and cognitive impairment.

**Cholesterol**

Since both high and low serum cholesterol have been associated with dementia\textsuperscript{33-37}, the evidence for an association between total cholesterol and cognitive function is ambiguous. Cholesterol may directly affect neurodegeneration\textsuperscript{38}, since in-vitro studies show that when statins are used cholesterol reduction leads to inhibition of the formation of amyloid-beta\textsuperscript{39}, the main constituent of amyloid plaques. Case-control studies investigating the effect of statins on the cognitive function also show that the use of statins protects against dementia\textsuperscript{10,11}. There is also indirect support for a connection between cholesterol and cognitive function via atherosclerotic disease. Since it has been suggested that atherosclerotic disease is associated with clinical and subclinical ischaemic diseases in the brain, which contributes to the development of late onset dementia\textsuperscript{9}. Clearly, studies with longitudinal designs should be done to determine if there is a causal association between cholesterol and cognitive function.

**Inflammation**

Observational studies have shown that the use of anti-inflammatory drugs lowers the risk for dementia and poor cognitive function\textsuperscript{10,11,40-42}. These studies could be biased, since physicians might not prescribe anti-inflammatory drugs to patients with dementia, however they do suggest a relation between chronic inflammation, dementia and poor cognitive function. Randomised clinical trials using anti-inflammatory drugs in subjects with dementia, however, did not show beneficial effects of these
drugs on cognitive function. However, these findings cannot refute that inflammation plays a role in dementia and poor cognitive function, since immune system proteins, such as the upregulation of adhesion molecules and pro-inflammatory cytokines in microglia cells, and the deposit of complement and C-reactive protein are found around amyloid plaques. Furthermore, it has been shown that patients with Alzheimer’s disease exhibit a pro-inflammatory response upon endotoxin stimulation in whole blood samples. However, the initiating event leading to neuro-inflammation, neurodegeneration, poor cognitive function and dementia remains unclear.

The aim of this thesis

The first aim is to test the hypothesis: "Is atherosclerosis the initiating event that leads to ischaemia in the brain and subsequently to neuro-inflammation, followed by neurodegenerative processes that ultimately results in cognitive impairment and dementia?" This hypothesis is based on findings from experimental animal studies investigating the effect of ischaemia and a pro-inflammatory response on stroke lesion. These studies revealed that blocking of the pro-inflammatory response after ligation of the middle cerebral artery markedly reduced the lesion size and improved neurological outcome. These findings suggest that the magnitude of ischaemic lesion size in the brain depends on the inflammatory response. It is therefore possible that subjects with atherosclerosis and a pro-inflammatory response have an increased ischaemic lesion size compared to subjects with atherosclerosis and an anti-inflammatory response. The difference in ischaemic lesion size subsequently leads to differences in cognitive function between subjects with a pro- or an anti-inflammatory response.

The second aim of this thesis is to investigate the association between the inflammatory response and atherosclerosis. Since elevated immune system proteins, such as C-reactive protein and fibrinogen are associated with atherosclerosis. The idea is that the inflammatory response directly or indirectly, via lipid and glucose metabolism, contributes to atherosclerosis. Since both insulin resistance and dyslipidemia are associated with systemic inflammation and atherosclerosis.

All studies presented in this thesis were performed within the Leiden 85-plus Study, a population based study in 85 year old citizens of Leiden. First, in this thesis the effect of “classical” cardiovascular risk factors and cardiovascular disease on cognitive function is described (figure 1). The effect of gender (chapter 3), high-density lipoprotein (chapter 5) and cardiovascular disease, i.e. atherosclerosis (chapter 4) on cognitive function is described in the so-called “classic” route (figure 1). Then data on the first aim of this thesis are presented in the so-called “alternative” route (figure 1), showing the relation between atherosclerosis, inflammation and cognitive function (chapter 6). Finally, two studies report on the second aim of this thesis, i.e. the association between the inflammatory response and atherosclerosis, by describing the relation between the “classic” route and the “alternative” route (figure 1). The first of these two studies shows the association between interleukin-10, a strong anti-inflammatory cytokine, type-2 diabetes and the metabolic syndrome, i.e. a clustering of cardiovascular risk factors, such as insulin resistance, dyslipidemia and hypertension (chapter 7). The second study describes the relation between atherosclerosis - that is cerebrovascular disease- (chapter 8) and inflammation.
Figure 1 Atherosclerosis, inflammation and cognitive function
Introduction

Definition and measurement of cognitive function and inflammation

Cognitive function

Some basic theoretical issues on cognitive function need to be discussed before exploring the effect of atherosclerosis and inflammation on cognitive function. Areas of cognitive function that tend to change as a result of (clinical) events include general cognitive speed, attention and memory. These are listed among the so-called fluid abilities. Many other cognitive domains are far less likely to change, e.g., reading, general knowledge, and language abilities. These are called crystallised abilities and, by definition, do not change much. In this thesis fluid abilities were determined, i.e. those cognitive function that tend to change when (clinical) events occur, by measuring cognitive speed and memory, using sophisticated neuropsychological tests. Cognitive speed, consisting of attention and processing speed, is the most discriminative measure because age-related cognitive decline first manifests itself by a decline in attention and processing speed. In the elderly, memory remains relatively intact until the late stages of cognitive decline, whereas cognitive speed declines more rapidly.

Inflammation

Tumour-necrosis factor-α (TNF-α) and interleukin-10 (IL-10) are two central inflammatory cytokines, which play a crucial role in the regulation of immune reactivity. TNF-α shows a wide spectrum of biological activities. It is a decisive pro-inflammatory mediator in the host defence to infection by activating the inflammatory host response thus increasing the proliferation of macrophages and lymphocytes. Furthermore, TNF-α inhibits anticoagulatory mechanisms and promotes thrombotic processes and therefore plays an important role in pathological processes such as venous thromboses and atherosclerosis. In the brain it promotes the proliferation of astroglia and microglia and may therefore be involved in neurodegenerative processes such as demyelinisation. IL-10 on the other hand is a central anti-inflammatory cytokine with strong deactivating properties on the inflammatory host response mediated macrophages and lymphocytes. And it potently inhibits the production of pro-inflammatory cytokines such as IL-6 and TNF-α.

In this thesis ex vivo whole-blood samples were simulated with 10 ng/ml of endotoxin (lipopolysaccharide) to determine TNF-α and IL-10 production capacity. This has been done since the ex-vivo production of TNF-α and IL-10 shows good reproducible patterns and because the production of both TNF-α and IL-10 is under tight genetic control. Approximately 60% of the variation in TNF-α production and 75% of the variation in IL-10 production is genetically determined.

Atherosclerosis

Two approximations to determine the burden of atherosclerosis were used. For the first approximation electrocardiograms were recorded on a Siemens Siccard 440 and transmitted by telephone to the ECG Core Lab in Glasgow for automated Minnesota coding. Codes 1-1, 1-2, and 1-3 were equated with a diagnosis of myocardial infarction. Codes 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3 represented subjects
with myocardial ischaemia. Subjects were classified as having atherosclerosis, whereas the electrocardiogram revealed signs of myocardial infarction or myocardial ischaemia. The classification from the Second Manifestations of ARTerials disease (SMART) study was used as a second approximation to determine the presence of atherosclerosis. Findings from the SMART study using this classification showed among other things that the severity of atherosclerosis (intima-media thickness and arterial stiffness) was related with the number of cardiovascular diseases obtained from the subject’s medical history. In the Leiden 85-plus Study, the history of cardiovascular disease was obtained from the general practitioner or the subject’s attending physician. Subjects were classified as having atherosclerosis, whereas a positive history of myocardial infarction, angina pectoris, arterial surgery, stroke, or intermittent claudication was present, or if the electrocardiogram revealed signs of myocardial infarction or myocardial ischaemia.
References
19 Vandenbroucke JP. How much of the cardioprotective effect of postmenopausal oestrogen is real? Epidemiology 1995; 6:207-08.
26 Folsom AR, Rasmussen ML, Chamless LE, et al. Prospective associations of fasting insulin, body fat...
51 Spera PA, Ellison JA, Feuerstein GZ, Barone FC. IL-10 reduces rat brain injury following focal stroke.
Introduction
