Vascular factors in dementia and apathy
Eurelings, Lisa

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
The number of individuals suffering from dementia is expected to rise significantly in the future as a result of the aging of the worldwide population. Given that so far no curative treatments have been developed, prevention remains paramount to reduce the global disease burden. A large body of evidence points to the direction of an important role of vascular factors in the aetiology of dementia. Recently, it has been estimated that up to a third of all Alzheimer’s disease cases can be attributed by potentially modifiable, mostly vascular risk factors, including hypertension, diabetes mellitus, smoking, obesity, and physical inactivity. It has been hypothesized that these risk factors could represent an important target for prevention of dementia in older individuals.

In Chapter 2 of Part I of this thesis we presented the findings from the Prevention of Dementia by Intensive Vascular Care (preDIVA) study. This is a large cluster-randomised controlled trial that was executed in primary care to assess whether nurse-led intensive vascular care can prevent or postpone dementia and all-cause disability in community-dwelling older adults. The intervention consisted of 4-monthly visits to a practice nurse for assessment and management of the cardiovascular risk profile by tailored lifestyle advice and, if necessary, initiation or optimisation of medical treatment. Individuals in the control group received care as usual. Follow-up duration was six to eight years and main secondary outcomes were all-cause mortality, the occurrence of cardiovascular events, depressive symptoms, and cognitive decline. Although the intervention resulted in a modest decrease of blood pressure and appeared to be safe, it did not lead to a reduction of the incidence of all-cause dementia, disability, or any of the other secondary outcomes. Secondary analyses suggested that the intervention was more effective in persons adherent to the intervention and in those with untreated baseline hypertension. A subgroup analysis for dementia type revealed that the occurrence of non-Alzheimer’s disease, of whom the majority of cases was diagnosed with vascular dementia, was lower in the intervention group, but the small number of cases in this analysis renders the interpretation of this finding difficult. It was concluded that the setting of the preDIVA study, characterized by a relatively high level of usual care, may have offered insufficient contrast between groups. A larger window of opportunity may be present in less developed countries with a lower standard of healthcare. Furthermore, the intervention may have been of insufficient intensity, suggesting that future dementia prevention studies may benefit from intensification of the intervention.

Vascular factors have also been assumed to contribute to the aetiology of symptoms of apathy in old age, which has been described in the “vascular apathy” hypothesis. This hypothesis was postulated in 2008 by van der Mast et al. based on the finding that vascular disease predicted apathy symptoms but not depressive symptoms in community-dwelling older individuals. Driven by the hypothesis that apathy symptoms, rather than depressive symptoms, could be a behavioural marker of underlying vascular disease, the
main aim of part II of this thesis was to assess whether symptoms of apathy and depression are differentially associated with future cardiovascular disease and stroke and to assess potential mechanisms underlying these relationships. All the studies described in part II of this thesis are embedded in the context of the preDIVA study with the exception of an individual participant data meta-analysis that used pooled data from a large number of longitudinal studies in community-dwelling older adults.

In chapter 3 we showed that apathy, but not depressive symptoms, were associated with an increased risk of cardiovascular disease in a large sample of community-dwelling older individuals without previous cardiovascular disease or stroke from the preDIVA study. This association was independent of demographical characteristics, presence of traditional cardiovascular risk factors, and depressive symptoms. No association was observed between either apathy or depressive symptoms and incident stroke. Given that presence of apathy may converge with an increased likelihood to withdraw from medical care, we concluded that clinicians should be vigilant to recognize these symptoms in older individuals. Furthermore, these findings strongly suggest that apathy symptoms should be differentiated from depressive symptoms in older individuals.

In chapter 4 we further explored these findings by evaluating in-depth the mediating role of cardiovascular risk factors in the relationship between symptoms of apathy and depression with incident cardiovascular disease using the same sample of community-dwelling older individuals. We used structural equation modelling (SEM) which enabled us to assess both the mediating role of cardiovascular risk factors in the relationship of apathy and depressive symptoms with incident cardiovascular disease (indirect effects), as well as the unique contribution of apathy and depressive symptoms to incident cardiovascular disease over and above what cardiovascular risk factors explain (direct effects). We found that physical inactivity, current smoking, and diabetes mellitus accounted for nearly a quarter of the association of apathy symptoms with incident cardiovascular disease, suggesting the importance of assessment and treatment of these risk factors in older individuals with apathy. The majority of this link could be attributed to other, yet unknown, mediators, leaving room for further research. Consistent with our findings reported in chapter 3, no association between depressive symptoms and incident cardiovascular disease was found.

In chapter 5 we explored whether apathy and depressive symptoms are differentially related to increased C-reactive protein (CRP) levels as a marker of low-grade inflammation in community-dwelling older individuals without previous cardiovascular disease or stroke from the preDIVA study. At three different time points, we found that symptoms of apathy rather than depressive symptoms were cross-sectionally associated with increased CRP levels. This association remained after adjustment for demographics and depressive symptoms and was only slightly attenuated after adjustment for cardiovascular risk factors. Baseline CRP did not predict the occurrence of apathy or
depressive symptoms after two or four years of follow-up. The consistent concomitant association of apathy symptoms with increased CRP levels led us to the conclusion that apathy symptoms may be a behavioural manifestation of concurrent low-grade inflammation, in line with “sickness behaviour”. Given that low-grade systemic inflammation is often associated with underlying atherosclerosis, these findings may provide an explanation why apathy symptoms are predictive of future cardiovascular disease. The absence of a relation with depressive symptoms further corroborates the importance of distinguishing both constructs.

In chapter 6 we report on the Initiative on CArdiovascular disease Risk and Apathy (ICARA) which we set up to externally validate our previous finding in preDIVA of a unique association of apathy symptoms with incident cardiovascular disease. By means of an individual participant data meta-analysis using pooled data from a large number of longitudinal studies in community-dwelling older adults we found that apathy symptoms were associated with future myocardial infarction, stroke, and all-cause mortality, independent of demographics, previous myocardial infarction and/or stroke, and the presence of depressive symptoms. These relationships seemed to be “dose-dependent” with an 88% increased mortality risk for individuals with the highest apathy score. Depressive symptoms were associated with future stroke and all-cause mortality, but not with future myocardial infarction. Given the independent associations of apathy symptoms with several patient-important outcomes, also in individuals without depressive symptoms, we concluded that recognizing apathy in older individuals is paramount. Moreover, the importance of discriminating both symptom types was again confirmed by the differential relationship with myocardial infarction.

In chapter 7 the main findings of this thesis are discussed in the context of the existing literature and potential clinical implications and directions for future research are described. In the discussion of part I it was described that at this point there is insufficient evidence to conclude that an intervention targeting vascular risk factors and lifestyle factors can prevent the onset of dementia in a general population of unselected older individuals. Future research could be aimed at evaluating whether vascular risk factor management can be effective in delaying or preventing the onset of dementia in individuals who are asymptomatic but at increased risk of dementia. Secondary analyses in preDIVA suggested a window of opportunity in persons with untreated baseline hypertension. Future multidomain dementia prevention studies may benefit from delivering interventions with a higher intensity at a younger age, most likely in midlife. During the conduct of these studies minimizing attrition and improving adherence to the intervention is essential. To ensure sufficient contrast between groups, this research is preferably conducted in settings with enough room for improvement with regard to level of cardiovascular care (e.g. in developing countries). Large-scale international collaborations could offer an opportunity to maximize pow-
In the discussion of part II the following main findings were discussed: A) Symptoms of apathy, but not of depression, were associated with an increased risk of cardiovascular disease in community-dwelling older individuals from the preDIVA study. This finding was replicated in a large meta-analysis of individual participant data. In this meta-analysis we furthermore observed that symptoms of apathy were associated with an increased risk of stroke and mortality, also in individuals without depressive symptoms; B) Nearly a quarter of the association of apathy symptoms with future cardiovascular disease that was found in the preDIVA study could be explained by the mediating role of diabetes mellitus, smoking, and decreased physical activity; C) In the preDIVA population, symptoms of apathy, but not of depression, were cross-sectionally associated with low-grade inflammation as measured by increased levels of C-reactive protein, which is often present in vascular disease. We discussed apathy both in terms of a risk marker for future cardiovascular disease (i.e. apathy as a behavioural marker of underlying (subclinical) vascular disease and inflammation) as well as a risk factor for future cardiovascular disease (for example through deleterious health behaviours and reduced adherence to medical treatment). Given the association of apathy symptoms with several patient-important outcomes, also in those without depressive symptoms, we concluded that it is necessary that clinicians are sensitive to this condition and that they are able to differentiate apathy from depression. Moreover, we suggested that future researchers should differentiate both conditions to be able to further clarify the underlying etiological mechanisms of apathy and depression and their differential role in the aetiopathogenesis of adverse clinical outcomes.