Vascular factors in dementia and apathy
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CHAPTER 7

GENERAL DISCUSSION
The central theme of the present thesis is the relationship of cardiovascular risk factors and cardiovascular disease with dementia and apathy. In Part I, the objective was to investigate whether a nurse-led, multidomain intervention targeting vascular risk factors could prevent or postpone the onset of dementia and disability in community-dwelling older individuals. This was assessed in the Prevention of Dementia by Intensive Vascular Care (preDIVA) trial which also formed the context for most of the observational studies described in Part II of this thesis. The main objective of Part II was to investigate the associations of apathy and depressive symptoms with future cardiovascular disease and stroke and to gain more insight into the mechanisms underlying these relationships.

In this chapter the main findings of this thesis will be summarized and discussed in the context of the current knowledge. Furthermore, clinical implications and directions for future research will be addressed.

**PART I**

**Vascular factors and dementia**

Observational studies have provided compelling evidence that particularly midlife vascular risk factors, including hypertension, diabetes mellitus, smoking, obesity, and hypercholesterolemia, are linked with an increased risk of dementia. Lifestyle factors including physical activity and healthy nutrition have been associated with a reduced risk of dementia. Furthermore, cohort studies have shown that treatment targeting several vascular risk factors, including antihypertensive treatment and statin use, is associated with a decreased risk of dementia.

On the basis of this large body of observational evidence suggesting an important role of vascular factors in the aetiology of dementia, and to overcome potential sources of bias such as confounding by indication, several intervention studies aimed at the prevention of cognitive decline or dementia have been performed during the past decades. Most of the intervention studies targeting a particular vascular risk factor have failed to find a protective effect or have yielded inconsistent results. Based on a review of all available scientific evidence for preventive interventions in dementia, the National Institutes of Health concluded that evidence is of insufficient strength, with an exception of some evidence for a beneficial effect of antihypertensive treatment. The Systolic Hypertension in Europe (Syst-Eur) study was the first randomised controlled trial (RCT) to show a considerable effect of blood pressure lowering therapy on the risk of dementia. After a mean follow-up of 3.9 years, anti-hypertension treatment was associated with a 55% decrease of dementia incidence in hypertensive subjects of 60 years and older. On the other hand, various other RCT’s did not convincingly demonstrate such an effect, and the Hypertension in the Very Elderly Trial cognitive function assess-
ment (HYVET-COG) meta-analysis of four RCT’s including the Syst-Eur trial reported a much smaller effect of anti-hypertension treatment on the prevention of dementia than observed in the Syst-Eur trial alone (HR 0.87 [95%-CI 0.76–1.00]).20 It is however important to note that these trials were primarily designed to assess the effect on cardiovascular outcomes such as stroke and coronary artery disease and used dementia and cognitive decline as secondary endpoints. Also, these trials tested unimodal therapies which, given the complex multifactorial aetiology of dementia, may not be as effective as preventive measures that target multiple risk factors simultaneously.

The preDIVA trial was the first study to test a multidomain intervention strategy using dementia as primary outcome.22,23 During the course of the preDIVA trial further support to the idea that blood pressure lowering therapy can reduce dementia risk was provided by results of the study of Norton et al. indicating that, after adjustment for interdependence between risk factors, approximately a third of all Alzheimer’s disease cases worldwide might be accounted for by potentially modifiable, mostly vascular risk factors.24 However, although systolic blood pressure decreased more in the intervention group and a subgroup analysis suggested that the intervention administered in preDIVA was associated with a decreased risk of non-Alzheimer’s disease, it did not appear to decrease the incidence of all-cause dementia or Alzheimer’s disease in particular. Nor did it affect the incidence of disability, mortality, or cardiovascular events. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), another recently completed multidomain trial, showed a small, statistically significant benefit of a 2-year intervention targeting vascular and lifestyle related risk factors as well as cognitive training on tests for global and executive cognitive function in individuals aged 60 to 77 years.25 However, it is unsure whether this treatment effect will eventually translate into the prevention of dementia after longer follow-up. This will be assessed in the 7-year follow-up of FINGER trial participants.26 Main results of the recently completed Multidomain Alzheimer Preventive Trial (MAPT) are still expected. This RCT evaluated the effect of nutritional guidance, physical exercise, cognitive training, and omega-3 supplementation during a period of three years on cognitive function in frail individuals aged 70 years and older.27

Thus, despite overwhelming observational evidence of a role of vascular factors in the aetiology of dementia, so far experimental studies have failed to demonstrate strong and consistent effects of vascular risk factor management to prevent dementia. Yet, vascular risk factor management, including lifestyle interventions, might still be of value in the prevention of dementia and cognitive decline, at least in certain subgroups, as was suggested by the results of the preDIVA study. Given that there is currently still no treatment available that can effectively slow down the dementia disease process, prevention probably remains the most important strategy to reduce the incidence and future prevention studies are desperately needed to counter the expected rise in
dementia prevalence. Although the possibility exists that there is no true causal relationship between vascular risk factors and the occurrence of dementia, the inconsistent and mostly neutral findings in previous trials could also be explained by methodological characteristics of the studies, including selection of study population, nature of the intervention, and type of outcome. Below some considerations are provided that researchers could take into account in designing and conducting their future dementia prevention studies.

**Considerations for future studies**

**Study population**

Evidence from epidemiologic studies suggests that particularly midlife vascular risk factors are strongly associated with late-life dementia.\textsuperscript{28-31} Associations with late-life risk factors are less robust\textsuperscript{1,32,33} and even inverse associations of blood pressure, serum cholesterol, and body mass index with dementia risk have been observed.\textsuperscript{1,34-36} Most intervention studies targeting vascular risk factors have been conducted in individuals of relatively old age and long-term randomised trials starting in midlife are lacking.\textsuperscript{22} Conceivably, one of the reasons for lack of strong effects in current trials, and potentially also the reason why a decrease in blood pressure did not translate into an effect on overall dementia incidence in preDIVA, is a suboptimal timing of the intervention, i.e. after the time window during which an intervention would be effective. This has also been observed in trials assessing the effect of hormone replacement therapy to prevent dementia and cognitive decline in women, with evidence of a decreased risk if oestrogen supplementation occurs in early post-menopause and an increased risk in late post-menopause supplementation.\textsuperscript{37} Determining the optimal window for preventive interventions is therefore of great importance, and although the exact age range is unknown, the optimal window for vascular risk factor management is likely in midlife.\textsuperscript{38}

Another important consideration with regard to the study population is determining the extent to which individuals should be at risk of dementia. If the objective is to find a prevention strategy that is effective for the prevention of late-life dementia, which is generally characterized by a heterogeneous aetiology,\textsuperscript{12} a population-based design, as was used in preDIVA, would be appropriate and would yield results that are generalizable. Also, although an intervention administered to a population at low or moderate risk may offer limited benefit to an individual, it can have considerable effect at the population level due to the large number of individuals at low and moderate risk, which is described in the so-called “prevention paradox”.\textsuperscript{39} If an intervention is developed that can delay the onset and progression of the disease by only one year, the number of Alzheimer’s disease patients worldwide could be reduced by approximately 9 million in 2050, along with a substantial decrease in the number of patients needing
high-care levels. These advantages of a truly population-based design are however offset by the need to recruit large sample sizes due to the low incidence of dementia in unselected populations. An alternative approach would be to only include individuals with early symptoms of cognitive impairment, but these symptoms may reflect presence of underlying brain pathology which may already be too advanced for an intervention to be effective. Therefore, it seems best to include asymptomatic individuals at high risk of dementia. One possibility is to base the selection on Alzheimer’s disease biomarkers such as amyloid-β and tau in cerebrospinal fluid, structural magnetic resonance imaging, and functional imaging using FDG-PET or amyloid-PET. However, if the selection strategy is focused too much on one neuropathological mechanism, other mechanisms which may also be of relevance in late-life dementia will not be addressed. Also, the test characteristics of most Alzheimer’s disease biomarkers are not fully understood at the general population level and the measurement is often expensive and sometimes also invasive which limits their use in large-scale studies. Another possibility to include asymptomatic individuals at increased risk of dementia is by selection of individuals with one or two copies of the apolipoprotein E (APOE) ε4 allele which is a major risk factor for dementia, but this type of selection raises ethical concerns given the emotional distress genetic risk disclosure may bring about. Alternatively, one could consider to apply a selection based on family history of dementia. The relative risk conferred by having a first degree relative is of similar magnitude as having one APOE ε4 allele (around 3) and increases with decreasing age of onset in the relative. In contrast to the measurement of APOE genotype, and also of biomarkers, selection based on family history constitutes a pragmatic and cheap selection strategy that enables to take into account multiple pathophysiological mechanisms at the same time. In preDIVA, some evidence was found for a beneficial effect of the intervention in participants with untreated hypertension at baseline, especially in those who were adherent to the intervention. This suggest that selection of individuals with untreated hypertension could also be an appropriate enrichment strategy.

**Nature of the intervention**

The aetiology of dementia and cognitive decline in old age is multifactorial with genetic, vascular, and lifestyle related risk factors which often co-occur and can have synergistic effects in determining the risk of dementia. Recently, it was estimated that a 10-20% relative reduction per decade in the prevalence of each of seven important risk factors (diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment) could reduce the prevalence of Alzheimer’s disease in 2050 by approximately 8-15% worldwide. This suggests that for an intervention to become effective, multiple risk factors should be targeted simultaneously, being multimodal in that it includes both pharmacological and non-pharmacological
components to improve vascular and lifestyle related risk factors. In health care systems of developed countries, many older individuals already use pharmacological agents to improve their cardiovascular risk profile according to existing guidelines for primary and secondary prevention and therefore the intervention should fit into these cardiovascular prevention programs.\(^{38}\) In addition, where possible, it should also be tailored to the risk profile of the individual. This requires an intervention that can be flexibly adjusted across different health care systems with different protocols for primary and secondary prevention.\(^{38}\)

An explanation for lack of a beneficial effect of the multidomain intervention within preDIVA on any patient-important-outcome could be that, due to the pragmatic nature of the trial, it was not intensive enough to yield sufficient contrast between groups. Although blood pressure decreased significantly more in the intervention group, no relevant effects were observed on other cardiovascular and lifestyle related factors. These findings suggest that to increase contrast between groups, multidomain interventions in future trials should be more intensive. In the FINGER trial, a very intensive and comprehensive intervention was administered including individual and group sessions to tailor the participant’s diet, individual and group sessions consisting of cognitive training, physical exercise sessions multiple times a week, and multiple visits to the study nurse and study physician to assess metabolic and vascular risk factors. In addition to a small improvement on a composite score based on tests for cognitive functioning, the intervention had beneficial effects on body mass index, dietary habits, and physical activity. On the basis of a low drop-out rate and high adherence the researchers concluded that the intervention was feasible within the trial.\(^{25}\) However, it remains questionable whether an intervention with this level of intensity is feasible and sustainable outside a research context. Probably a balance should be sought between a pragmatic intervention with a relatively low intensity, but on the other hand with high external validity, as was administered in preDIVA, and a comprehensive and intensive intervention with a higher likelihood of yielding sufficient contrast between groups as delivered in FINGER.

Sensitivity analyses in preDIVA suggested lower hazard ratios for individuals that were adherent to the intervention, implying that more efforts should be made to improve adherence to the intervention in future trials. During the preDIVA trial a qualitative study was performed in current and former participants and this revealed that a personal relationship with the study nurse and a coaching and supportive approach, including the opportunity for the participant to be actively involved without being patronized, were important motivators for participation.\(^{48}\) Delivering the intervention using motivational interviewing could therefore be an important strategy to improve these aspects\(^{49}\) and future studies should consider incorporating this into their design. Frequent changes of the nursing staff appeared to be an important barrier to participation in preDIVA\(^{28}\) which underlines the necessity of continuity of care that forms the basis
of a personal relationship. The French ACCEPT study currently investigates reasons for non-adherence in dementia prevention studies and this is expected to yield further insights to improve adherence to the intervention in future studies.\textsuperscript{50}

**Outcome measure**

In ongoing and previous trials generally one of the following types of endpoints were used: incident dementia or Alzheimer’s disease, incident mild cognitive impairment due to Alzheimer’s disease, cognitive function or decline, and biomarker changes.\textsuperscript{22} Dementia or Alzheimer’s disease would be the most clinically meaningful endpoint, but the long lag time between an intervention in midlife and the age at which dementia usually manifests itself renders the conduction of a traditional RCT difficult. As a solution, it has been suggested to separate the intervention and measurement of the outcome in time with the outcome assessment being delayed several years to decades after the intervention has finished.\textsuperscript{38} However, this type of design makes it difficult to directly link the outcome to the intervention given that multiple co-interventions could have been administered in the window between the administration of the intervention and the measurement of the outcome. Alternatively, rather than choosing one of the four above mentioned variables as outcomes, a shift towards a trajectory perspective could be made in which the development of dementia is approached as a continuum. In doing so, the focus would be on measurement of disease progression by assessment of cognitive decline combined with measurement of biomarkers, in addition to the assessment of dementia as a clinical endpoint. This approach would also enable to further unravel the potential predictive value of especially biomarkers, but also of cognitive decline, for the occurrence of dementia.\textsuperscript{13,22} Given the by default long duration of this type of study (i.e. intervention in midlife and late-life dementia as final endpoint), the question arises whether this type of research is feasible in terms of financial resources. This requires that funding bodies need to be convinced of the value of this type of trajectory research.

**Setting**

Most of the current evidence for vascular risk factor management to prevent dementia stems from trials conducted in countries with a high level of care.\textsuperscript{51} In the Netherlands, cardiovascular prevention has gained importance in general practice during the past years. In 2006, the same year as the start of the preDIVA trial, the Dutch College of General Practitioners (NHG) issued the cardiovascular risk management guideline which enables identification of individuals at high risk of cardiovascular disease by using the “SCORE-Netherlands”.\textsuperscript{52} This is a risk estimation tool based upon the presence of specific risk factors in an individual. Although the SCORE risk estimation model as used in the original 2006 guideline was only applicable to individuals with a maximum age of 65 and a later revised version to individuals with a maximum age of 70,\textsuperscript{53} this guideline
has also resulted in an increased attention for cardiovascular prevention in individuals over the age of 70. In 2011, the NHG introduced the guideline “PreventieConsult module Cardiometabool Risico” (Prevention Consultation cardiometabolic risk)\(^{54}\) as a supplement to the existing guidelines on cardiovascular prevention, which is aimed at the assessment of the risk of cardiovascular disease, type II diabetes mellitus, and nephropathy in individuals of 45 years and older. This guideline describes a pro-active and systematic approach to identify individuals at increased risk and focuses on individuals up to the age of 85. In addition to the introduction of new guidelines, nurse-led cardiovascular risk management programs have been initiated and, as part of the “Nationale Programma Ouderenzorg”, several programs aimed at improving care of frail elderly have been introduced.\(^{55}\) These new developments in general practice and health care in general that took place during the course of the preDIVA trial may very likely have attenuated the contrast between both study groups.

In contrast, in low- and middle income countries age-specific rates of cardiovascular disease are increasing rapidly which is mostly attributable to urbanization, westernization of diet and increasing rates of cardiovascular risk factors.\(^{56}\) Combined with a suboptimal delivery of cardiovascular care, this leads to an increasing burden of cardiovascular disease.\(^{57}\) Also, due to fast growth in the elderly population in developing countries, a major increase of the world dementia prevalence rate is expected to take place here.\(^{58}\) Already two-thirds of all people with dementia live in these countries, which is in sharp contrast with the 10% of all dementia research that is performed there.\(^{51}\) Future trials could explore whether cardiovascular risk management programs can be effective in preventing or delaying the onset of dementia in this type of setting, based on a larger window of opportunity, at least with regard to level of cardiovascular care.

Selective drop-out

Selective drop-out is one of the major sources of selection bias in longitudinal dementia studies. If the reason for drop-out is related to both the treatment condition and the outcome (i.e. dementia) effect estimates can be distorted in such a way that an association is masked or even reversed.\(^{59}\) It is conceivable that this type of bias is not rare in dementia research, given that multiple health related conditions, including cognitive decline, may influence both the ability and willingness to continue study participation and the risk of dementia. Thus, often missing data are not at random, i.e. missing of information on dementia status is dependent upon the status itself, and statistical methods such as classical multiple imputation fall short.\(^{59,60}\) To prevent biased effect estimates, achieving complete follow-up is therefore paramount. This was the main reason to retrieve the drop-outs in preDIVA by performing a minimal functional assessment. The importance of this effort became evident by the observation that 6.6% of the retrieved participants appeared to be demented (3.4% in control group and 3.3% in intervention...
group) and 16.4% deceased (6.8% in control group and 9.6% in intervention group). The importance of retrieving drop-outs is also underlined by an analysis performed in the Systolic Hypertension in the Elderly Program (SHEP) Study which suggested that selective drop-out masked a potential protective effect of anti-hypertensive treatment on cognitive decline.\(^6\) In the first place, future studies should try to minimize attrition. This could be done by employing motivational interviewing techniques and by ensuring continuity of care as was suggested by the qualitative analysis in preDIVA.\(^4\) Nevertheless, if attrition does occur, continuous efforts will be needed to retrieve drop-outs.

Another important source of selection bias is selective survival. Both cognitive decline and dementia are associated with an increased risk of illness and death.\(^5\) Incident cases will be missed if an individual with dementia dies before cognitive evaluation has been performed during a periodic follow-up visit. This implies that also for deceased individuals the cognitive status during life should be retrieved, as was done in the preDIVA study.

### Power and sample size

Performing realistic power calculations in dementia prevention trials has proven difficult.\(^1\) Often calculations have been based on findings from larger observational studies with a longer period of follow-up leading to underpowered trials with high risk of type II errors.\(^1\) Although in preDIVA the power calculation was based on experimental evidence derived from the Syst-Eur trial, this calculation may not have been realistic either. Power was calculated based on an expected between-group difference of 33% in the cumulative incidence rate of dementia, which in turn was based on the 55% risk reduction observed in the Syst-Eur trial. In retrospect, the Syst-Eur trial may have yielded too optimistic results regarding the effectiveness of blood pressure control on dementia incidence. Later meta-analyses reported much smaller effects of antihypertensive treatment with risk reductions ranging from 2% to 13%.\(^2,6\) In addition, the observed dementia incidence (7.0%) within the control group of the preDIVA trial was lower than anticipated (8.2%), even in spite of extended follow-up in some of the participants. This might be explained by the recently suggested decline in age-specific dementia incidence in high-income countries.\(^6\) The problem of an unrealistic power calculation may also have occurred in the HYVET-COG trial that also based their power calculation on results of the Syst-Eur trial and found a non-significant effect of antihypertensive treatment on the risk of dementia.\(^2\) Researchers of future trials assessing the effect of multidomain vascular care on the prevention of dementia should therefore perform more realistic power calculations. This could be done by combining data from the recently completed experimental multidomain studies with dementia as primary or secondary endpoint (i.e. FINGER and preDIVA). Furthermore, in their power calculations researchers should take into account the suspected decline in age-specific incidence of dementia.\(^6\)
The sample size needed to have enough power to detect significant effects of an intervention is heavily dependent on age because the incidence of dementia rises sharply with age. Richard et al. calculated required sample sizes for a dementia prevention study depending on the age of individuals, different follow-up times, and different rates of risk reduction. For example, to obtain a significant hazard ratio of 0.85 of an 8-year intervention administered in individuals below the age of 70 one would require a sample size of 22125 individuals. Although a smaller number would be needed for an intervention study with cognitive decline as outcome, the above suggested trajectory approach would still need a large sample size, because the power analysis has to be based on the incidence of dementia and not on the incidence of cognitive decline preceding the onset of dementia. To maximize power, large-scale international collaborations are needed. This would also enable harmonization of study design, data collection and analysis to render findings more comparable and to eliminate an important modifiable source for inconsistency. In 2011, the European Dementia Prevention Initiative has been set up which is an investigator-initiated initiative that aims to identify the most effective dementia prevention strategies by combining data from the three multidomain studies PreDIVA, MAPT and FINGER. Furthermore, this initiative has obtained funding from the European Union under the 7th Framework Program for setting up the international Healthy Ageing Through Internet Counselling in the Elderly Study. This is a prevention study that uses an innovative internet-based intervention strategy to optimize management of older individuals with multiple cardiovascular diseases and risk factors with cognition as a secondary endpoint. Future initiatives could be set up at the global level to further facilitate raising funds to conduct large-scale, long-term studies to study the effect on dementia as a final endpoint, which would be clinically the most relevant.

**Vascular risk factor management in old age**

Thus far, evidence is insufficient to conclude that an intervention aimed at vascular risk factors and lifestyle factors can prevent the onset of dementia in a general population of unselected older individuals. However, lack of evidence of effectiveness does not necessarily imply evidence of lack of effectiveness. If the lack of evidence of effectiveness was mainly due to insufficient power, it might well be possible that adding the results of the PreDIVA study to the above mentioned HYVET-COG meta-analysis of studies of anti-hypertensive treatment to reduce dementia risk (HR 0.87 [95%-CI 0.76–1.00]) will yield a significant result. Pooling of the PreDIVA data with these trials is defendable since antihypertensive treatment was a main component of the multidomain intervention in preDIVA and the intervention did yield a significant effect on blood pressure. Furthermore, vascular risk factor management has been shown to be relevant.
in old age for other reasons than dementia. For individuals up to the age of 80 years there is convincing evidence that cholesterol lowering medications reduce the risk of cardiovascular morbidity and mortality.\textsuperscript{66} Regarding blood pressure lowering therapy these effects have even been observed in individuals of 80 years and older.\textsuperscript{67} Also, adherence to a healthy lifestyle has been associated with a reduced risk of other chronic conditions, including diabetes mellitus and cancer.\textsuperscript{68} An analysis of the baseline data in preDIVA revealed that 63\% of individuals had two or more risk factors amenable to treatment and that more than one-third of the individuals had a systolic blood pressure of 160 mmHg or higher.\textsuperscript{69} This suggests that, despite the already relatively high level of vascular care delivered in the Netherlands, there is still a considerable window of opportunity for prevention and that continuous efforts are needed to improve cardiovascular risk management in older individuals. This is especially important given the expected increase in the prevalence of obesity and diabetes mellitus.\textsuperscript{70,71} In contrast to earlier fears of negative effects of blood pressure reduction on cognition,\textsuperscript{72} the preDIVA data suggested that a multidomain intervention targeting vascular risk factors can be safely administered in old age.

Additional research is necessary to evaluate 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. The preDIVA data suggested a window of opportunity in individuals with untreated baseline hypertension. Future multidomain prevention studies may yield stronger effects if interventions with a higher intensity are delivered at a younger age, most likely in midlife. Continuous efforts should be made to minimize attrition and improve adherence. This research is preferably conducted in settings with enough room for improvement with regard to level of cardiovascular care to ensure sufficient contrast between groups. Finally, international collaborations are needed to maximize power, improve generalisability and harmonization of methodology, and combine efforts in raising large-scale funds.

**PART II**

**The concept of apathy and its assessment**

The term apathy derives from the Greek word "apatheia" which was used by the Stoic philosophers to denote a condition of being without feelings and passions.\textsuperscript{73} At that time, the condition was considered a desirable state because rationality was deemed the main human attribute and emotions would hinder clear thinking.\textsuperscript{73} Over time, the meaning of the term has frequently changed and by the time of the nineteenth century the term was used to indicate a state of non-responsivity,\textsuperscript{73} more compatible with our current pejorative view of the construct. However, the exact nosological position of ap-
Apathy is still a frequently debated issue. Until the nineties of the last century apathy was merely considered as a symptom occurring in the context of several neuropsychiatric conditions. Marin was the first to propose that apathy can also occur as a syndrome in its own right. In 1991, Marin developed criteria for the syndrome of apathy and considered lack of motivation as its core feature. According to the criteria, lack of motivation had to be evidenced by all three of the following: diminished goal-directed behaviour (e.g. lack of effort, lack of productivity), diminished goal-directed cognition (e.g. lack of interest), and diminished emotional concomitants of goal-directed behaviours (e.g. unchanging affect, lack of emotional responsivity to positive or negative events). The lack of motivation ought not to be attributable to emotional distress, intellectual impairment, or diminished level of consciousness. In 2001, these criteria were adapted by Starkstein et al. to enhance applicability. First, the requirement of absence of emotional distress and intellectual impairment was omitted. Second, Starkstein et al. included the requirement of the symptoms to cause clinically significant distress or impairment in important areas of functioning and the requirement that the symptoms are not caused by the direct physiological effects of a substance. A second adaptation of the criteria was made by Starkstein and Leentjes in 2008 by inclusion of the requirement of the symptoms to be present for at least 4 weeks during most of the day. That same year, a task force including members of three professional organizations and experts from Europe, Australia and North America was set up in order to reach final agreement and develop consensus criteria with a higher level of acceptance. These consensus criteria followed the same structure as the criteria adapted by Starkstein et al., but instead of the requirement of presence of at least one symptom in each of the three domains (behaviour, cognition, emotion), this was reduced to at least one symptom in at least two of the three domains. Furthermore, the requirement that symptoms should not be exclusively explained or due to physical or motor disabilities was added to exclude conditions that mimic apathy. These consensus criteria have been validated in patients with Parkinson’s disease and in a group of patients with a variety of neuropsychiatric diseases.

An important topic in the nosological discussion is the differentiation of apathy from depression. Although apathy can be a symptom of depression, it can also occur independently from depression. Starkstein et al. showed that 23% of Alzheimer’s disease patients with apathy did not have concomitant depression and Marin et al. even found 55% of apathetic Alzheimer’s disease patients not to be depressed. Furthermore, apathy has been found to occur in isolation in Parkinson’s disease patients and patients with stroke. Isolated apathy can be characterized by lack of motivation in the absence of dysphoric symptoms including a depressed mood, guilt, suicidal ideation, hopelessness, and helplessness. There is also evidence for different neuropathological and neurochemical substrates of both conditions. Autopsy and neuroimaging
studies in Alzheimer’s disease patients show that apathy is predominantly associated with neuropathology in the frontal subcortical circuits, especially the anterior cingulate and the dorsolateral prefrontal cortex,\textsuperscript{86,87} whereas depression is mainly related to neuropathology in the frontal-striatal and subcortical limbic circuits including the locus ceruleus, substantia nigra, hippocampus, hypothalamus.\textsuperscript{87} Neurochemically, apathy may be more related to cholinergic deficits and depression to serotonergic deficits or a dopamine and norepinephrine imbalance.\textsuperscript{87}

Although the task force that developed the diagnostic consensus criteria for apathy emphasized the importance of distinguishing apathy from depression,\textsuperscript{76} depression was not explicitly mentioned as one of the exclusion criteria. Potentially, ever since the requirement that apathy should not be attributable to emotional distress was omitted from the criteria postulated by Marin the differentiation with depression has become more difficult. Recently, Pagonabarraga et al. proposed a stepwise approach to diagnose apathy using a new set of clinical diagnostic criteria.\textsuperscript{85} The first step (A) is to assess apathy based on criteria that pertain to symptoms including loss of initiative, blunted affect, and lack of interest and concern. In the second step (B), the presence of depressive symptoms such as helplessness, hopelessness, sadness, and suicidal ideation is assessed. The third step (C) is aimed at assessing presence of cognitive impairment by evaluation of planning, memory, attention, and concentration. The use of this stepwise approach enables the clinician to differentiate between isolated apathy (A), apathy associated with depression (A+B), and apathy associated with cognitive impairment (A+C). The developers suggest that each of the three types of apathy has a different underlying pathophysiology which may be useful in tailoring treatment approaches to the individual patient with apathy. These criteria, however, still need to be validated.

Related to the diversity of diagnostic criteria is the diversity of instruments that are used to measure apathy. The Neuropsychiatric Inventory (NPI) is one of the most frequently used scales, but has not been developed to specifically measure apathy.\textsuperscript{88} Scales that have been developed to specifically measure apathy as a syndrome include the Apathy Evaluation Scale (AES) developed by Marin,\textsuperscript{74} the Apathy Scale developed by Starkstein (an abridged version of the AES),\textsuperscript{89} the Inventoire Apathie (IA) developed by Robert,\textsuperscript{90} and the Lille Apathy Rating Scale (LARS).\textsuperscript{91} A problem with all these instruments is a lack of a gold standard which renders it difficult to assess content validity. The studies performed in the context of this thesis have used three items of the 15-item Geriatric Depression Scale (GDS-15)\textsuperscript{92} to assess symptoms of apathy. These items are: (1) Have you dropped many of your activities and interests?; (2) Do you prefer to stay at home, rather than going out and doing new things?; and (3) Do you feel full of energy?. Several principal component analyses have identified these three items as a separate apathy-related subdomain within the GDS-15\textsuperscript{93,94} and face validity has been established.\textsuperscript{95} However, the items do not cover all three domains (i.e. diminished
goal-directed behaviour, cognition, and emotion) described in the consensus criteria developed by Robert et al.\textsuperscript{76} It seems that the emotional domain is lacking within the 3-item apathy subscale of the GDS-15 (GDS-3A). This implies that a formal diagnosis of apathy according to the consensus criteria could not be established in our studies and we therefore refer to apathy symptoms throughout our studies in this thesis. An advantage of the lack of the emotional domain within the GDS-3A may be that when apathy symptoms are analysed in the context of low endorsement of the remaining 12 mood-related items of the GDS-15, as was done in our analyses, it is unlikely that we assessed apathy symptoms as part of depression.

The unique role of apathy in cardiovascular disease and inflammation

In addition to individuals with neuropsychiatric diseases, apathy can also occur in older individuals from the general population.\textsuperscript{95-98} In the individual participant data meta-analysis of 47625 older persons that was performed in the context of the Initiative on CArdiovascular disease Risk and Apathy (ICARA) (chapter 6), we showed that apathy symptoms were present in 31.1\% of community-dwelling individuals and isolated apathy symptoms, i.e. without concomitant depressive symptoms, in 13.8\% of individuals. In the introduction of this thesis we described that apathy has been associated with a history of cardiovascular disease, stroke, and cardiovascular risk factors\textsuperscript{93} and that vascular disease has been found to predispose for apathy symptoms, but not depressive symptoms.\textsuperscript{95,99} Based on these findings we hypothesized that apathy symptoms, rather than depressive symptoms, could be a marker of underlying vascular disease and would therefore also be predictive of new cardiovascular disease and stroke. In line with this hypothesis, we observed in the present thesis research that apathy symptoms, but not depressive symptoms, increased the risk of cardiovascular disease in community-dwelling older individuals from the preDIVA study (chapter 3). This finding was replicated in the individual participant data meta-analysis. (Isolated) apathy symptoms increased the risk of future myocardial infarction both in individuals with and without a history of vascular disease, whereas no association was found for (isolated) depressive symptoms (chapter 6). Altogether these findings lend support for the notion that apathy symptoms, more so than depressive symptoms, are a behavioural manifestation of underlying (subclinical) vascular disease and therefore a risk marker for future cardiovascular disease.

Further support for the notion of apathy as a risk marker comes from our findings in the preDIVA sample that specifically apathy symptoms, but not depressive symptoms, were associated with low-grade inflammation as expressed in increased levels of C-reactive protein (CRP) (chapter 5), which often co-occurs with vascular disease.\textsuperscript{100} In line with this, Groeneweg-Koolhoven et al. recently observed that higher CRP levels independently correlated with apathy among non-depressed older persons. In addition,
Apathy was associated with presence of cardiovascular disease in these individuals.\textsuperscript{101} In the population-based Hoorn study, increased levels of CRP predicted reduced information processing speed, attention, and executive functioning,\textsuperscript{102} which are all frequent neuropsychological correlates of apathy.\textsuperscript{86,103} Based on these findings, a parallel can be drawn between apathy and sickness behaviour. Originally, sickness behaviour has been considered an adaptive cytokine-induced response to infection which is normally reversible after pathogen clearance.\textsuperscript{104} In case of chronic low-grade inflammation, sickness behaviour may represent a maladaptive, possibly non-reversible, behavioural response including apathy-like symptoms of somnolence, loss of energy, malaise, and diminished interest in activities. Consistent with this hypothesis and supporting the idea of apathy being a risk marker of vascular disease, Johansson et al. observed that inflammation mediated the relationship between impaired cardiac function and sickness behaviour which was defined as a symptom cluster consisting of anhedonia, fatigue, and sleepiness.\textsuperscript{105}

Radiological evidence may also point into the direction of apathy, rather than depression, being a behavioural risk marker of underlying vascular disease. Hollocks et al. found apathy, but not depression, to be associated with reductions in white matter integrity in individuals with small vessel disease\textsuperscript{106} and van Grool et al. observed that, independently of depression, apathy symptoms were associated with diffuse loss of both grey and white matter volumes in a non-demented older population.\textsuperscript{107}

In addition to being a risk marker, apathy may also be considered a risk factor for future cardiovascular disease. A structural equation model analysis of the preDIVA data showed that nearly a quarter of the association of apathy symptoms with future cardiovascular disease was mediated by the cardiovascular risk factors diabetes mellitus, smoking, and decreased physical activity (chapter 4). These findings suggest a causal pathway between apathy symptoms and cardiovascular disease via deleterious health behaviours and diabetes mellitus. In this model no association was found between depressive symptoms and future cardiovascular disease (chapter 4). The finding of Yao et al. that apathy without major depression has negative effects on leisure-time physical activity in community-dwelling older persons is also consistent with the conception of apathy as a risk factor.\textsuperscript{108} Furthermore, due to its nature, apathy may act as a risk factor by causing withdrawal from medical care and reduced treatment adherence.

Interestingly, in contrast to future myocardial infarction, no differential association of apathy and depressive symptoms with future stroke was found in the individual participant data meta-analysis. Both apathy and depressive symptoms were associated with an increased risk of stroke (chapter 6). This may indicate the involvement of different etiologic mechanisms in myocardial infarction and stroke. The relative contribution of low-grade inflammation, which we found to be related to apathy but not depressive symptoms (chapter 5), may be greater for myocardial infarction than for stroke, given
the more heterogeneous aetiology of stroke, including selective carotid artery disease, cerebral small vessel disease, and atrial fibrillation.

**The relationship of apathy and depressive symptoms with blood pressure**

Moonen et al. have provided an overview of the literature regarding the association of blood pressure with depression in old age and describe that both low and high levels of blood pressure have been associated with depression in older individuals. According to Moonen et al. these inconsistent findings could be explained by differential relationships of blood pressure with distinct symptom domains of depression. As an indication for this hypothesis Moonen et al. provide the example of two cross-sectional reports in older individuals that reported low blood pressure to be specifically associated with low positive affect but not with negative affect, which according to Moonen et al. has been shown to correlate with apathy. Thus, in old age, mood related symptoms may be particularly related to lower levels of blood pressure, whilst apathy symptoms may be more related to higher levels of blood pressure. Consistent with this, in our SEM analysis of the preDI-VA data we observed that symptoms of apathy were positively associated with systolic blood pressure, whereas mood-related symptoms were inversely associated with systolic blood pressure (chapter 4). In a cross-sectional analysis in a cohort of depressed older individuals Moonen et al. observed that individuals with higher systolic blood pressure, diastolic blood pressure, and mean arterial pressure had higher scores on the Apathy Scale. Inconsistent results were observed regarding the relationship of blood pressure with mood symptoms; only a higher systolic blood pressure was associated with more mood symptoms, but no association was found for higher levels of diastolic blood pressure or mean arterial pressure. It was concluded by the authors that the association of higher blood pressure with depression in old age may be mainly driven by symptoms of apathy. According to the authors higher blood pressure may lead to localized cerebral lesions that specifically increase the risk of apathy, rather than depressive symptoms.

However, in a sample of community-dwelling older individuals with mild cognitive dysfunction and lower functional ability of the Discontinuation of Antihypertensive Treatment in Elderly People (DANTE) study, lower blood pressure measures were associated with more symptoms of apathy. In participants with higher functional ability no association was found between blood pressure measures and symptoms of apathy. These findings suggest that the association between blood pressure and symptoms of apathy is moderated by functional ability. Although the authors stress that no causal inferences could be made due to the cross-sectional design of the study, they suggest that lower levels of blood pressure in older individuals with lower functional ability may increase the risk of apathy symptoms by compromising cerebral perfusion as a result of a failing vascular system.
Clinical implications

In 1998, Fones was the first to cast doubt on the vascular depression hypothesis. Since then an increasing number of studies addressed the distinction between apathy and depression, both conceptually and clinically. As described above, there is substantial evidence that apathy has a unique relationship with several biological correlates including cardiovascular disease, both clinically and radiologically, blood pressure, and inflammation, supporting the notion of apathy as a separate construct. In addition, these findings might suggest that the vascular depression hypothesis may have been confounded by the concept of apathy and that at least in some individuals what has previously been considered vascular depression may in fact represent vascular apathy. Clinicians should therefore be sensitive to apathy, especially since people with symptoms of apathy are more likely to withdraw from medical care. Importantly, apathy needs to be considered not only in those with a history of vascular disease but also in those without such a history. We found that also in individuals without previous vascular disease apathy symptoms were associated with an increased risk of cardiovascular events, stroke, and mortality, independently of depressive symptoms (chapter 3 and 6). Both in the case of apathy being a marker of underlying (subclinical) vascular disease and in the case of apathy acting as a risk factor for vascular disease through deleterious health behaviours and other cardiovascular risk factors, these findings suggest that in older individuals with apathy evaluation of the cardiovascular risk profile may be important, regardless of their cardiovascular history. Recognition of apathy and differentiation from depression may also be important from a treatment perspective. For example, treatment with serotonin re-uptake inhibitors (SSRIs) may be effective for depression, but seems ineffective for apathy or, even worse, could aggravate the condition. However, at present, research on the effectiveness of pharmacological treatments with apathy as primary outcome is sparse and the existing evidence is limited to individuals with neuropsychiatric disease. In dementia best results have been observed for acetylcholinesterase inhibitors and in Parkinson’s disease there is evidence for a beneficial effect of dopamine agonists. In addition, a variety of non-pharmacological psycho-social interventions has been tested, but mainly in the context of dementia, and results are not clear-cut. Identification of apathy may also be important for psychoeducation to caregivers of individuals with apathy. Caregivers who do not recognize apathy as a neuropsychiatric condition may misperceive the apathetic behaviour of their proxy as laziness, stubbornness, or unwillingness, potentially leading to frustration and resentment. In addition, tailored support to caregivers to manage the situation can prevent under- or overstimulation of the apathetic individual.
Directions for future research

In general, to be able to accurately identify individuals with apathy, the availability of a valid assessment instrument is essential. So far, the diagnostic accuracy of the GDS-3A that we used in our studies has been assessed in three study populations that all used the Apathy Scale as reference instrument. In all study populations the specificity of the GDS-3A was high (ranging from 85.0% to 92.6%) but the sensitivity appeared to be dependent on the population under study. Sensitivity was low in two studies with relatively younger older individuals (29.3% and 32.8%) and higher in a study including the oldest old (69.0%). This difference may be related to a higher prevalence of apathy in the oldest old population. Although under the premises of non-differential misclassification the GDS-3A may well be suited for use in research on the association of apathy with determinants and outcomes, the relatively high percentage of false negatives in the youngest old implies that in clinical practice the GDS-3A may not be an appropriate screening instrument in this population. Given the clinical importance of detection of apathy, future research efforts should be aimed at the construction of screening tools with both a high level of specificity and sensitivity that are at the same time user-friendly. Preferably future studies should apply these tools.

Future studies should continue to differentiate apathy from depression in order to further clarify the underlying etiological mechanisms of both constructs and their differential role in the aetiology of adverse outcomes including cardiovascular disease and stroke. Unravelling the substrates of apathy may also be of importance to develop effective treatments. Given that apathy is a frequent neuropsychiatric symptom in older individuals from the general population, this research should also focus on individuals without neurodegenerative diseases. If adequate treatments for apathy are developed it could be assessed whether treatment of apathy can reduce the risk of future cardiovascular disease and stroke, which would further support the notion of apathy as a risk factor. From the risk marker perspective, it is currently still unknown whether treatment of vascular risk factors and vascular disease reduces the risk of apathy. The preDIVA trial would form an excellent context to study this research question by evaluating whether intensive vascular risk factor management compared to regular care can prevent or postpone the occurrence of apathy in individuals who were free of apathy at baseline.

A large number of studies have assessed the role of neuropsychiatric symptoms in the prediction of the onset of cognitive decline and dementia. Many of these studies show an important role of apathy and motivational symptoms of depression in the onset of cognitive decline, dementia, and the progression from cognitive decline towards dementia. Apathy could be an early feature of underlying neurodegenerative brain changes, i.e. it could be a prodromal feature of dementia. Furthermore, in line with the sickness behaviour hypothesis, symptoms of apathy could appear as a behavioural
Of underlying vascular disease and inflammation, two conditions that are both strongly associated with an increased risk of cognitive decline and dementia.\textsuperscript{126-128} Finally, apathy symptoms could act as a true causal risk factor by increasing the risk of cognitive decline and dementia through deleterious health behaviours or represent a reaction to awareness of early cognitive problems. The preDIVA trial can provide an opportunity to further study the differential role of apathy and mood-related symptoms in the prediction of cognitive decline and dementia and would enable to provide more insight into the role of vascular factors, health behaviours, and inflammation in this trajectory. The preDIVA data could also be used to further explore the potential moderating role of functional impairment as assessed with the Academic Medical Center Linear Disability Score\textsuperscript{129} in the association between symptoms of apathy and level of blood pressure. Furthermore, the longitudinal relationship of blood pressure with symptoms of apathy and the influence of blood pressure lowering medication could be assessed using these data.

Finally, it is currently unknown how the temporal stability of apathy symptoms or the lack thereof influences the predictive value of apathy symptoms for adverse vascular outcomes and mortality. Both the ICARA project and the preDIVA trial could serve as an excellent source to shed more light on the temporal stability of apathy, factors that are associated with a high level of stability and the influence thereof on the prediction of vascular events and mortality.
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