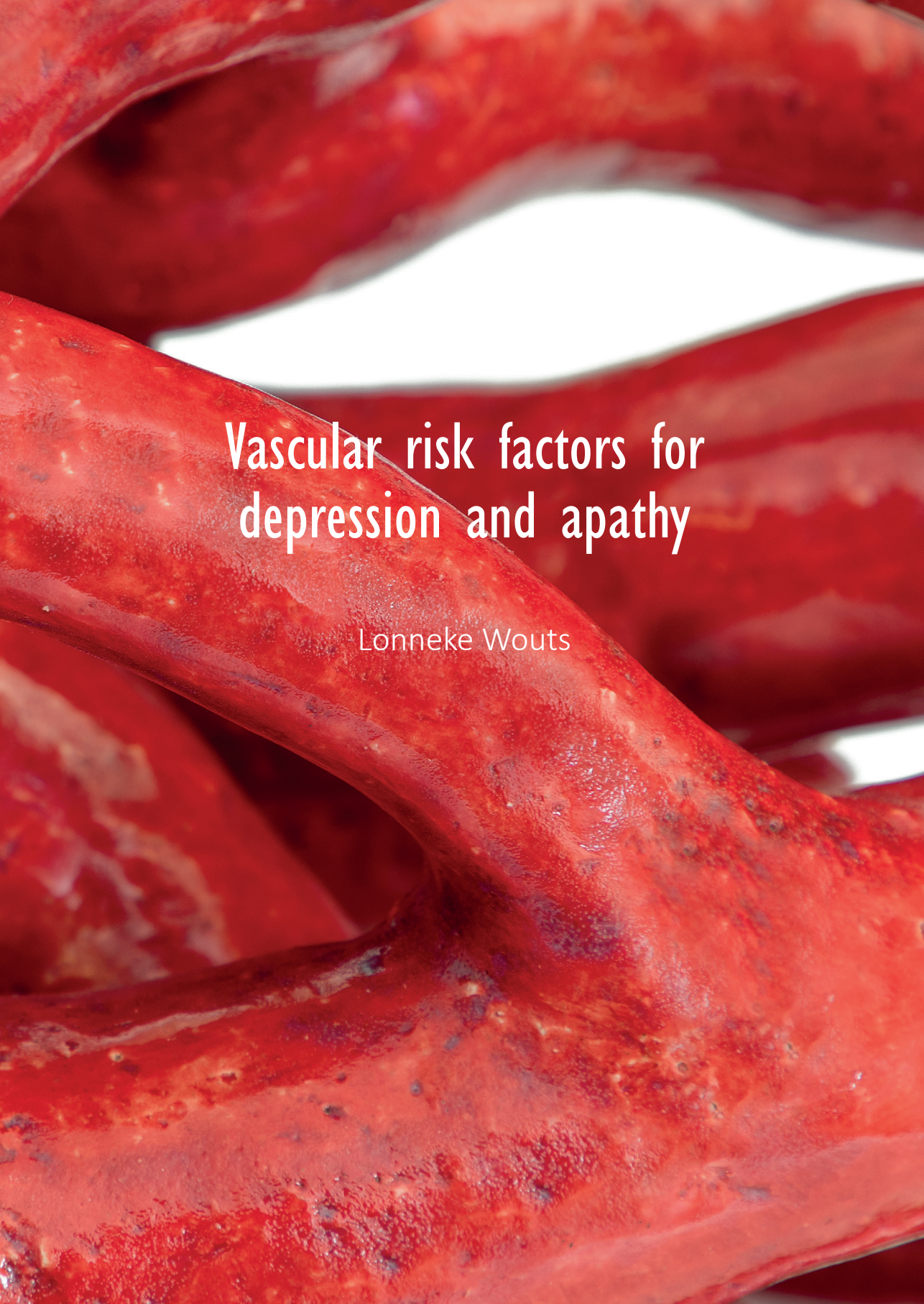


# Vascular risk factors for depression and apathy

Lonneke Wouts

# Vascular risk factors for depression and apathy

Lonneke Wouts

*Photography, design and lay-out*
Paulien Varkevisser | fotografie & vormgeving, Nijmegen
www.paulienvarkevisser.com

*Printing*
Ipskamp Printing B.V., Enschede, the Netherlands

rijksuniversiteit
groningen

# Vascular risk factors for depression and apathy

**Proefschrift**

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

donderdag 20 april 2023 om 12.45 uur

door

**Lonneke Wouts**

geboren op 24 juni 1977
te Tilburg

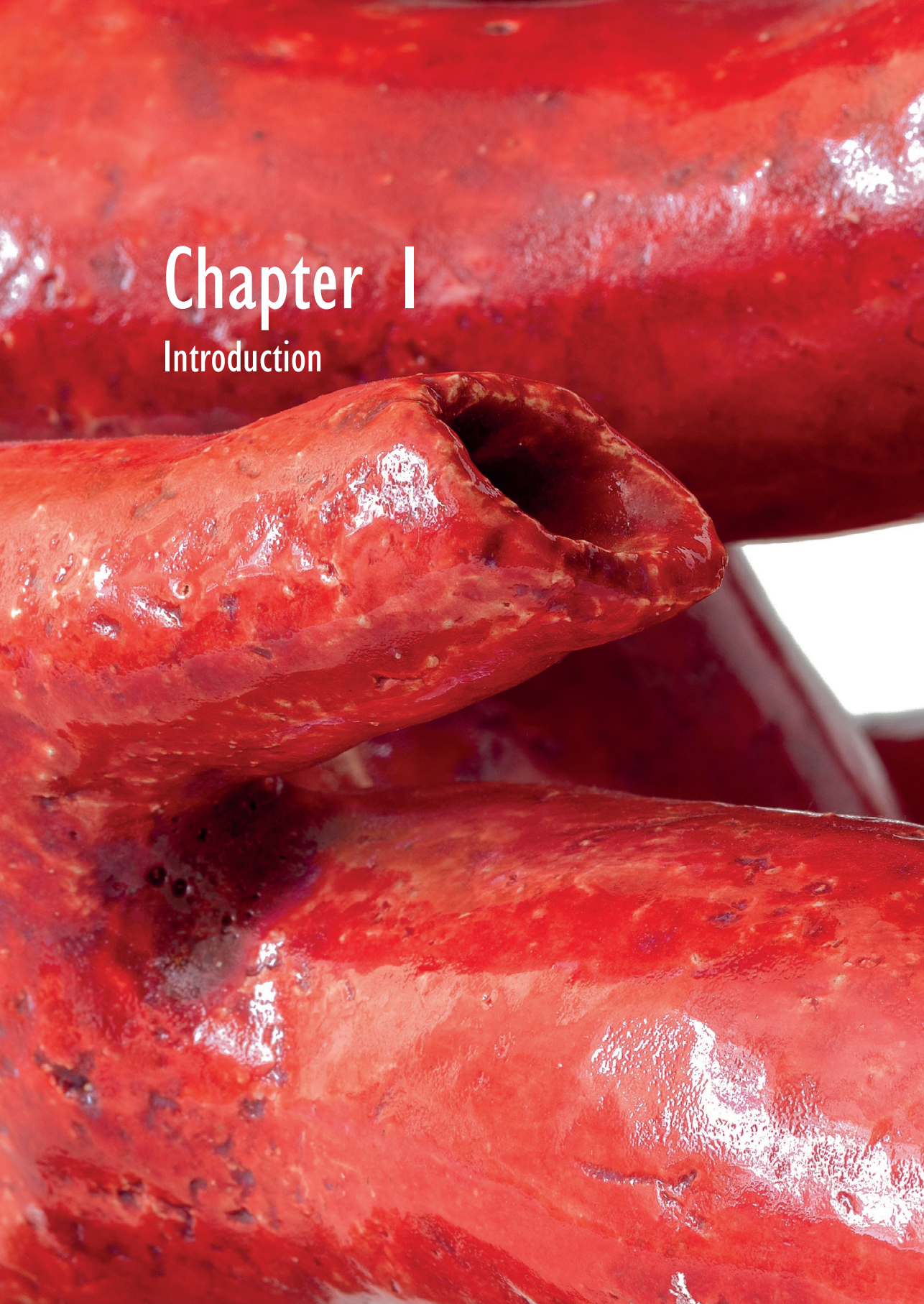
**Promotores**
Prof. dr. R.C. Oude Voshaar
Prof. dr. A.T.F. Beekman

**Copromotor**
Dr. R.M. Marijnissen

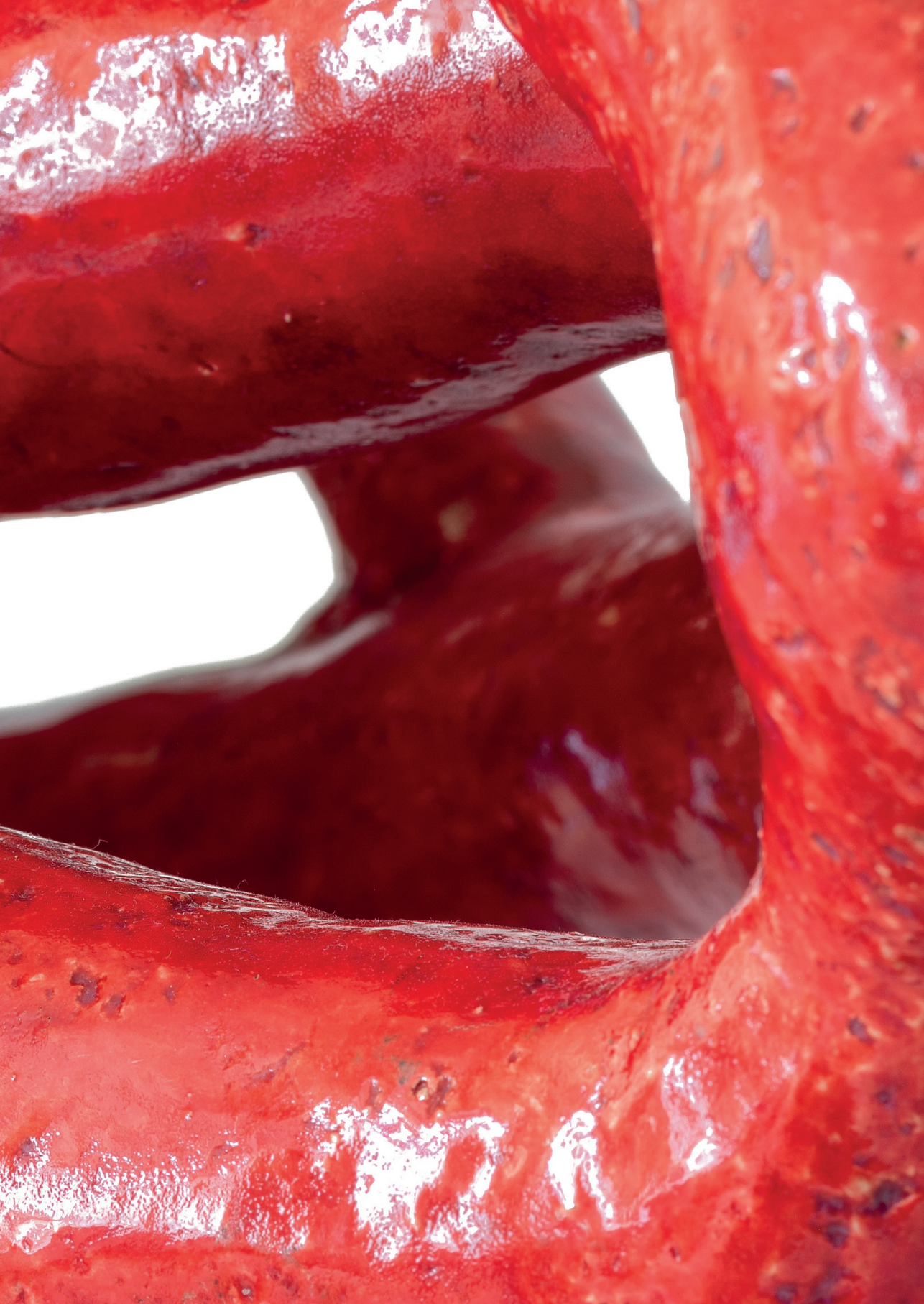
**Beoordelingscommissie**
Prof. dr. R.A. Schoevers
Prof. dr. B.C. van Munster
Prof. dr. F. Verhey

*Beeld:*
Helma Wouts-Meeuwissen, keramiek

# TABLE OF CONTENTS



# Chapter I
## Introduction



## Late-life depression

Depression is one of the most common and disabling psychiatric disorders in later life. Box 1 presents the diagnostic criteria for a major depression. The prevalence of major late-life depression ranges between 0.9-9.4% for those living in private households and between 14-42% for those living in institutions [1], where it needs to be noted that subthreshold depression (i.e. when older adults suffer from depressive symptoms without meeting the full criteria for a major depression) is even more prevalent [2]. The risk of becoming depressed in later life is raised in women and in individuals with a somatic illness, cognitive or functional impairment, lack or loss of social contacts and/or a history of depression [1]. In fact, besides the risks that are particularly common in late life (e.g. somatic disease and functional and cognitive impairment), all risk factors for depression across a person's lifespan can play a role in the development of late-life depression, also risk factors such as genetic predisposition, early life trauma and social stress that are typically associated with early-onset depression [3].

In elderly persons coping with depression, particularly in those suffering from severe depression, chronic disease and loneliness, the risk of chronicity is higher than it is in younger depressed individuals [4]. Antidepressant treatments, electroconvulsive therapy (ECT) and psychotherapy can be effective in older people [5], but often late-life depression goes unrecognized and untreated [6]. In those who do receive treatment for their depression, older age, more severe and longer duration of the depression, comorbid anxiety, physical illness and executive dysfunction predict a worse outcome [7].

The consequences of major and subthreshold depression in late life are severe: depressed elderly persons not only suffer from the depression itself, they also use more health care, particularly other types of health care than mental health care, and experience higher levels of functional and cognitive impairment and a lower quality of life, while their caregivers experience a high burden [8]. Also, the risk of mortality is elevated in late-life depression [9], part of which is explained by a raised cardiovascular [10 11] and cerebrovascular mortality [12].

***Depression diagnostic criteria (DSM-5)***

The individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure (core criteria). Collectively, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

1. Depressed mood most of the day, nearly every day.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

## Vascular depression or a depressive-executive subtype of late-life depression?

This clustering of vascular risks, vascular disease and depression in later life that clinicians frequently observed was confirmed in large epidemiological studies of late-life depression, whose findings prompted research into the potential relationships between depression and cardio- and cerebrovascular disease [13]. Objectives were to try and confirm that depression was a causal risk factor for vascular disease, and to identify the underlying pathophysiological mechanisms of this relationship. Another field of research focused on questions regarding the causes and consequences of the raised risk of a depressive disorder in post-myocardial infarction [14] and post-stroke patients [15].

Could it be that, not only recognized but also unrecognized or 'silent' vascular disease was a risk factor for and even a cause of late-life depression, and, if so, through what mechanisms? Neuroimaging studies showed an association between white matter hyperintensities (WMH), a marker of cerebral small vessel disease (CSVD; for more details, see the *CSVD and vascular apathy hypothesis* section), and depression [16]. Clinically, CSVD-related depression was linked to executive dysfunction and therapy resistance, leading to the inception of the vascular depression hypothesis [17]. The proposed pathophysiological mechanism for this vascular subtype of depression was disruption of the fronto-striatal pathways of the brain by CSVD [17].

Research into biological aging processes promoted a further differentiation of late-life depression syndromes, and provided information about the biomarkers with which they can be distinguished [18] (see Table1). The depression-executive dysfunction subtype of late-life depression is the only subtype that has been related to vascular risk and vascular disease and a higher risk of dementia [19]. In clinical practice and compared to depressed older adults without executive deficits, those with the depression-executive dysfunction syndrome more often present with reduced fluency, impaired visual naming, paranoia, loss of interest in activities, and psychomotor retardation but with a milder vegetative syndrome [20]. Moreover, treatment response is lower and the rate of recurrence is higher. Still, comprising antidepressants, ECT and/or psychotherapy, in essence treatment regimens for this subtype do not differ from those prescribed for a general depressive disorder [5]. Moreover, since a distinct clinical syndrome and a causal relationship between CSVD and depression could not be established, the name 'vascular depression' was abandoned by most researchers and clinicians [21 22].

*Table 1. Biomarkers and behavior associated with late-life depression subtypes*

| **Aging process** | **Biomarkers** | **Typical Phenotype** |
|---|---|---|
| Cerebral small vessel disease (CSVD) | Systolic blood pressure<br>Pulse wave velocity<br>Vessel calcification<br>White matter hyperintensities (WMH)<br>Fractional anisotropy in fronto-striatal tracts | Depressive-executive dysfunction |
| Inflammation and dopamine depletion | Interleukin-6 (IL-6)<br>Tumor necrosis factor alpha (TNF-alpha)<br>C-reactive protein<br>Dopamine D1/D2 receptor density<br>Dopamine transporter (DAT) activity<br>Response to stimulation | Inflammation, slowness |
| Oxidative stress and mitochondrial aging | F2 isoprostanes<br>$VO_2$ max<br>Enzymatic activity<br>IH MRS lactate<br>IH MRS N-acetyl aspartate<br>31P MRS phosphocreatine | Frailty, fatigue |

Adapted from: [18] Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. J Gerontol A Biol Sci Med Sci 2017; 72:343–52. https://doi.org/10.1093/GERONA/GLW241.

Although the association between WMH (as biomarkers for CSVD) and depression was confirmed in a meta-analysis [16], WMH are particularly related to those items of depression scales that gauge motivational problems such as loss of interest and psychomotor

retardation [23]. Accordingly, several studies have suggested that it might not be the depressive disorder but rather comorbid apathy that is related to CSVD [24] and to executive dysfunction [25].

## Apathy

Being part of many neurological and psychiatric diseases, apathy is a transdiagnostic symptom [26] but it can also be a stand-alone syndrome. Characterized by reduced activity, thought and emotions, it clearly overlaps with definitions of motivational constructs. The consequences of apathy are serious as it reduces quality of life [27] and causes more functional impairment [28], while increasing the caregiver burden [29 30]. Apathy is, moreover, associated with a higher risk of incident cardiovascular disease, stroke and mortality [31] and dementia [32].

***Apathy diagnostic criteria (2018)***

CRITERION A:
a quantitative reduction of goal-directed activity (behavioural, cognitive, emotional or social) in comparison to the patient's previous level of functioning

CRITERION B:
at least 2 of the 3 following dimensions for at least 4 weeks

B1 BEHAVIOUR AND COGNITION:
reduced general level of activity; diminished persistence of activity; less interest or slow in making choices; less interest in external issues; less interest in own health and image

B2 EMOTION:
less spontaneous emotion; fewer emotional reactions to the environment; less concern about the impact of actions/feelings on others; less empathy; less use of verbal or physical expressions

B3 SOCIAL INTERACTION: less spontaneous social initiative; less environmentally stimulated social interaction; decreased interest in interactions with family members; less verbal interaction; being more homebound

CRITERION C:
These symptoms cause clinically significant impairment in functioning

CRITERION D:
The symptoms are not solely attributable to physical or motor disabilities, a diminished level of consciousness, substance use or major changes in the patient's environment

*Adapted from: Robert P, Lanctôt KL, Agüera-Ortiz L, Aalten P, Bremond F, Defrancesco M, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. Eur Psychiatry 2018; 54:71–6. https://doi.org/10.1016/J.EURPSY.2018.07.008.*

There are a number of validated scales to assess apathy across populations, of which the Neuropsychiatric Inventory (NPI) and the Apathy Evaluation Scale (AES) are the most robust [33]. One of the problems that arise from the use in research, however, is that respondents with minimal cognitive impairment (MCI) or dementia tend to report lower apathy levels than peers without these health problems, which tendency is most likely attributable to less cognitive insight [34]. Most researchers investigating cognitively impaired populations hence prefer to use clinician or caregiver reported scales. Research into apathy has also benefitted from more uniformity through the recent consensus on the diagnostic criteria for apathy [35], which can be used in neuropsychiatric as well as healthy populations. Applying these well-defined criteria [35] in a range of neuropsychiatric disorders, researchers documented apathy prevalences of 55% for Alzheimer's disease, 70% for mixed dementia, 43% for minimal cognitive impairment, 27% for Parkinson's disease, 53% for schizophrenia and 94% for major depressive disorder [26]. Given that in the general population it is seen in 2-6%, apathy is predominantly a syndrome of old age, with the prevalence increasing with age, especially in men [36].
Treatment options for apathy are primarily aimed at raising the activity level through external stimuli and at relieving the caregiver burden [37] since the evidence for the efficacy of pharmacological interventions in apathy is not well established and confined to specific populations. Thus, there is some evidence for the usefulness of methylphenidate for the treatment of apathy in patients with Alzheimer's disease [38] and of dopamine agonists and rivastigmine in patients with Parkinson's disease [39].

## The neuroscience of apathy

Neuroimaging studies show that, across brain disorders, apathy is associated with abnormalities in the fronto-striatal pathways, most notably disruptions of the dorsal anterior cingulate cortex, the ventral striatum and connected brain regions [40]. Functional MRI and diffusion tensor imaging (DTI) studies have revealed that when the disruption in these fronto-striatal pathways leads to disruption of the underlying reward network, higher levels of apathy are seen [41] (See Figure 1). Research into this reward network and its function in the motivation process is emerging [42]. Studies combining functional MRI or DTI and behavioural paradigms show that the reward network plays a role in effort-based decision-making, i.e. the process in which a person decides whether to expend effort to gain a reward or not [42]. In people with CSVD, apathy is associated with reduced connectivity in this specific network of the brain [43].

## CSVD and the vascular apathy hypothesis

The prevalence of CSVD increases with age, from 5% in people aged 50 to almost 100% in those older than 90 years [44], with 52% of those with CSVD on neuroimaging showing apathy [24]. CSVD refers to a group of atherosclerotic diseases of the small vessels of the brain causing ischaemic changes in the surrounding brain tissue. MRI-markers of CVSD include white matter hyperintensities (WMH), cerebral microbleeds, lacunar infarcts

and visible perivascular spaces [45]. Clinically, CSVD can be silent (without observable symptoms) or present as a variety of geriatric syndromes like cognitive impairment, bladder dysfunction, or problems with gait and balance. Individuals with CWVD have a higher incidence of depression, strokes, dementia, disability and death [44 45].
Since apathy is associated with CSVD [24], and this association is independent of depression, the nature of this relationship has received increasing attention in the last few decades. This research has generated the vascular apathy hypothesis that expresses the notion that silent CSVD can cause apathy by disrupting the fronto-striatal pathways [46 47 48].

*Figure 1. Fronto-Striatal Pathway and Reward Network*

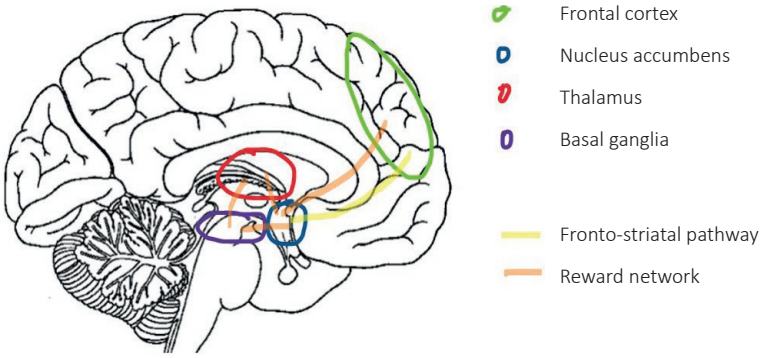
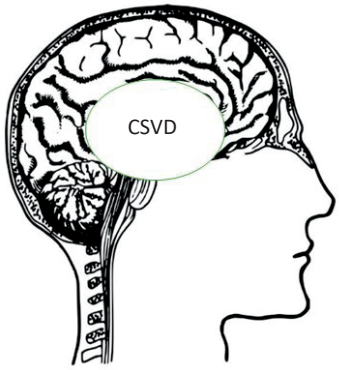



*Figure 2. Proposed Clinical Symptoms of CSVD*

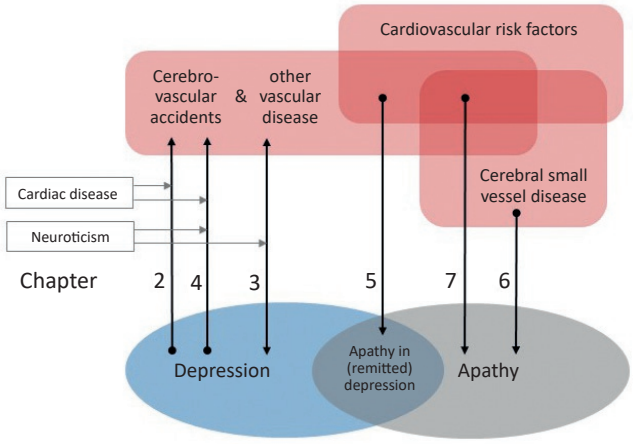



| | |
|---|---|
| Cognition | **Subcortical vascular MCI / Subcortical vascular dementia**<br>↓ *semantic memory*<br>↓ *executive/attentional functioning*<br>↓ *visuospatial functioning*<br>↓ *perceptual skills* |
| Neuropsychiatric | **Vascular apathy?**<br>↓ *emotion*<br>↓ *thoughts*<br>↓ *initiative*<br><br>**Depressive-executive sutype of depression**<br>*loss of interest*<br>*psychomotor retardation*<br>*paranoia*<br>↓ *fluency and visual naming* |
| Bladder dysfunction | |
| Gait | **Vascular parkinsonism**<br>*postural instability*<br>*falls*<br>*parkinsonian-ataxic gait* |

This model has given rise to new research questions. Is CSVD indeed a relevant causal risk-factor for apathy? Can CSVD be a sole cause of apathy and is CSVD-related apathy a recognizable and distinguishable clinical syndrome as using the term 'vascular apathy' suggests? These are all questions that lie at the heart of the research brought together in this doctoral thesis.

## Scope and objectives of the thesis

*Figure 3. Schematic representation of thesis outline*




The overall aim of the work presented here is to examine the associations between cerebrovascular disease with either depression or apathy in more depth. Figure 3 provides a schematic overview of the associations that are considered in the research documented in this thesis that consists of two parts. In the first part, we will be looking at the strength and nature of the relationships between cerebrovascular disease and depression and whether and how vascular risk and neuroticism interact in this relationship. In the studies presented in the second part, we investigate the strength and nature of the relationships between cerebrovascular disease, particularly CSVD, and apathy, where we evaluate the concept of vascular apathy as well as associations between CSVD and apathy in (remitted) depression.

## Part I

In the study prescribed in **Chapter 2** we asked ourselves: is depression associated with incident stroke and is this risk conditional upon the presence of cardiac disease? We sought to answer this question within the framework of the Longitudinal Aging Study

Amsterdam (LASA) in which depression as assessed at baseline is monitored and related to the incidence of stroke during a 9-year follow-up. We deemed this relevant as several studies have shown, albeit not consistently, that depression is a risk factor for stroke, [49] and because depression is not (yet) included as a well-established risk factor in stroke prevention guidelines [50]. Of note here is that previous studies may have been limited by the measures they used to diagnose depression and/or stroke. And, even though cardiac disease is one of the main risk factors for stroke, none explored whether this putative risk is conditional upon the presence of cardiac disease. Our study tries to overcome these shortcomings by including cardiac disease as effect modifier, by taking depression severity and chronicity into account, and finally by assessing stroke using a composite measure based on self-report data, medical records of GPs and death certificates.

In **Chapter 3** the research question we posed was whether the risk of depression on future stroke is conditional upon depressive symptoms related to underlying vascular disease and not upon depressive symptoms associated with high neuroticism? This study was again conducted as part of LASA, extending the study reported on in Chapter 2. We now assume that vascular depression, defined as depression etiologically linked to vascular disease, increases the risk of stroke, where depression that is etiologically related to high neuroticism does not. If confirmed, the presence of underlying (silent) vascular disease could confound the association between depressive symptoms and stroke, which would then explain the differences observed in populations with cardiac disease and without cardiac disease.

The objective of the study presented in **Chapter 4** was to explore whether neuroticism and vascular disease interact as risk factors for depression? Since higher levels of neuroticism and vascular disease often co-occur in individuals coping with late-life depression, not only the impact of each of these vulnerability factors but also their interactions are of interest. We will be examining the presence and nature of such interactions in a population-based survey called the Nijmegen Biomedical Study (NBS). Since neuroticism aggravates the impact of life events and has been related to a poorer adherence to (vascular) treatment we expect to find a positive interaction by which neuroticism exacerbates the impact of vascular disease on depression

## Part II

In the second part of this thesis, the focus is on associations between cerebrovascular disease and apathy. In the study reported in **Chapter 5** our aim was to elucidate whether apathy after remitted depression is related to cerebral small vessel disease (CSVD)? We anticipated to find associations between the severity of apathy and vascular risk factors and diseases in adults with a remitted depressive disorder who participated in the Netherlands Study of Depression and Anxiety (NESDA) and the Netherland Study of Depression in Older Persons (NESDO). We assumed that this association would not be explained by the residual symptom of a depressed mood, which we explicitly corrected for.

**Chapter 6** comprises a systematic review of studies investigating whether subclinical CSVD is associated with apathy in the general population? Apathy studies will be included in which CSVD is defined as white matter hyperintensities (WMH) or white matter diffusivity changes, lacunar infarcts, cerebral microbleeds, decreasing cortical thickness and/or perivascular spaces. We also considered studies with peripheral proxies for CSVD, i.e. the ankle brachial index, intima media thickness, cardio-femoral pulse wave velocity, hypertension or cardiovascular disease.

Our final study presented in **Chapter 7** explores whether CSVD can be a (sole) cause of apathy? The vascular apathy hypothesis is evaluated in depth in a narrative review in which the Bradford-Hill criteria are applied to distinguish between association and causation. We will use the results to determine whether vascular apathy can indeed be considered a distinct clinical syndrome, while reflecting on the pros and cons of the use of the term 'vascular apathy'.

## References


1. Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. *Acta Psychiatr Scand*. 2006;113(5):372-387. doi:10.1111/J.1600-0447.2006.00770.X

2. Meeks TW, Vahia I V., Lavretsky H, Kulkarni G, Jeste D V. A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *J Affect Disord*. 2011;129(1-3):126-142. doi:10.1016/J.JAD.2010.09.015

3. Colman I, Ataullahjan A. Life course perspectives on the epidemiology of depression. *Can J Psychiatry*. 2010;55(10):622-632. doi:10.1177/070674371005501002

4. Jeuring HW, Stek ML, Huisman M, et al. A Six-Year Prospective Study of the Prognosis and Predictors in Patients With Late-Life Depression. *Am J Geriatr Psychiatry*. 2018;26(9):985-997. doi:10.1016/J.JAGP.2018.05.005

5. Kok RM, Reynolds CF. Management of Depression in Older Adults: A Review. *JAMA*. 2017;317(20):2114-2122. doi:10.1001/JAMA.2017.5706

6. Horackova K, Kopecek M, Machů V, et al. Prevalence of late-life depression and gap in mental health service use across European regions. *Eur Psychiatry*. 2019;57:19-25. doi:10.1016/J.EURPSY.2018.12.002

7. Tunvirachaisakul C, Gould RL, Coulson MC, et al. Predictors of treatment outcome in depression in later life: A systematic review and meta-analysis. *J Affect Disord*. 2018;227:164-182. doi:10.1016/J.JAD.2017.10.008

8. Zivin K, Wharton T, Rostant O. The economic, public health, and caregiver burden of late-life depression. *Psychiatr Clin North Am*. 2013;36(4):631-649. doi:10.1016/J.PSC.2013.08.008

9. Penninx BWJH, Geerlings SW, Deeg DJH, Van Eijk JTM, Van Tilburg W, Beekman ATF. Minor and major depression and the risk of death in older persons. *Arch Gen Psychiatry*. 1999;56(10):889-895. doi:10.1001/archpsyc.56.10.889

10. Penninx BWJH, Beekman ATF, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001;58(3):221-227. doi:10.1001/ARCHPSYC.58.3.221

11. Wei J, Lu Y, Li K, Goodman M, Xu H. The Associations of Late-life Depression with All-cause and Cardiovascular Mortality: The NHANES 2005-2014. *J Affect Disord*. Published online December 2021. doi:10.1016/J.JAD.2021.12.104

12. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA*. 2011;306(11):1241-1249. doi:10.1001/JAMA.2011.1282

13. Teper E, O'Brien JT. Vascular factors and depression. *Int J Geriatr Psychiatry*. 2008;23(10):993-1000. doi:10.1002/GPS.2020

14. Leung YW, Flora DB, Gravely S, Irvine J, Carney RM, Grace SL. The impact of premorbid and postmorbid depression onset on mortality and cardiac morbidity among patients with coronary heart disease: meta-analysis. *Psychosom Med*. 2012;74(8):786-801. doi:10.1097/PSY.0B013E31826DDBED

15. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis. *Ageing Res Rev*. 2019;50:102-109. doi:10.1016/J.ARR.2019.01.013

16. Rensma SP, van Sloten TT, Launer LJ, Stehouwer CDA. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2018;90:164-173. doi:10.1016/J.NEUBIOREV.2018.04.003

17. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963-974. doi:10.1038/mp.2013.20

18. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. *J Gerontol A Biol Sci Med Sci*. 2017;72(3):343-352. doi:10.1093/GERONA/GLW241

19. Alexopoulos GS, Kiosses DN, Klimstra S, Kalayam B, Bruce ML. Clinical presentation of the "depression-executive dysfunction syndrome" of late life. *Am J Geriatr Psychiatry*. 2002;10(1):98-106. doi:10.1097/00019442-200201000-00012

20. Vilalta-Franch J, López-Pousa S, Llinàs-Reglà J, Calvó-Perxas L, Merino-Aguado J, Garre-Olmo J. Depression subtypes and 5-year risk of dementia and Alzheimer disease in patients aged 70 years. *Int J Geriatr Psychiatry*. 2013;28(4):341-350. doi:10.1002/GPS.3826

21. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report- a critical update. *BMC Med*. 2016;14(1). doi:10.1186/s12916-016-0720-5

22. Culang-Reinlieb ME, Johnert LC, Brickman AM, Steffens DC, Garcon E, Sneed JR. MRI-defined vascular depression: a review of the construct. *Int J Geriatr Psychiatry*. 2011;26(11):1101-1108. doi:10.1002/GPS.2668

23. Grool AM, Van Der Graaf Y, Mali WPTM, Witkamp TD, Vincken KL, Geerlings MI. Location and progression of cerebral small-vessel disease and atrophy, and depressive symptom profiles: the Second Manifestations of ARTerial disease (SMART)-Medea study. *Psychol Med*. 2012;42(2):359-370. doi:10.1017/S0033291711001383

24. Hollocks MJ, Lawrence AJ, Brookes RL, et al. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain*. 2015;138(12):3803-3815. doi:10.1093/brain/awv304

25. Lohner V, Brookes RL, Hollocks MJ, Morris RG, Markus HS. Apathy, but not depression, is associated with executive dysfunction in cerebral small vessel disease. *PLoS One*. 2017;12(5). doi:10.1371/journal.pone.0176943

26. Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry*. 2011;26(2):158-165. doi:10.1002/GPS.2508

27. Groeneweg-Koolhoven I, de Waal M, van der Weele, GM Gussekloo J, van der Mast R. Quality of life in community-dwelling older persons with apathy. *Am J Geriatr Psychiatry*. 2014;22(2):186-194.

28. Burton RL, O'Connell ME, Morgan DG. Cognitive and Neuropsychiatric Correlates of Functional Impairment Across the Continuum of No Cognitive Impairment to Dementia. *Arch Clin Neuropsychol*. 2018;33(7):795-807. doi:10.1093/ARCLIN/ACX112

29. Tsai CF, Hwang WS, Lee JJ, et al. Predictors of caregiver burden in aged caregivers of demented older patients. *BMC Geriatr*. 2021;21(1). doi:10.1186/S12877-021-02007-1

30. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al. Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. *Parkinsonism Relat Disord*. 2015;21(6):629-634. doi:10.1016/J.PARKRELDIS.2015.03.024

31. Eurelings LSM, van Dalen JW, ter Riet G, et al. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data. *Clin Epidemiol*. 2018;10:363-379. doi:10.2147/CLEP.S150915

32. Van Dalen JW, Van Wanrooij LL, Moll Van Charante EP, Brayne C, Van Gool WA, Richard E. Association of Apathy With Risk of Incident Dementia: A Systematic Review and Meta-analysis. *JAMA psychiatry*. 2018;75(10):1012-1021. doi:10.1001/JAMAPSYCHIATRY.2018.1877

33. Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, Marin RS. Are the available apathy measures reliable and valid? A review of the psychometric evidence. *J Psychosom Res*. 2011;70(1):73-97. doi:10.1016/J.JPSYCHORES.2010.01.012

34. Guercio BJ, Donovan NJ, Munro CE, et al. The Apathy Evaluation Scale: A Comparison of Subject, Informant, and Clinician Report in Cognitively Normal Elderly and Mild Cognitive Impairment. *J Alzheimers Dis*. 2015;47(2):421-432. doi:10.3233/JAD-150146

35. Robert P, Lanctôt KL, Agüera-Ortiz L, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *Eur Psychiatry*. 2018;54:71-76. doi:10.1016/J.EURPSY.2018.07.008

36. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int psychogeriatrics*. 2010;22(3):426-436. doi:10.1017/S1041610209991335

37. Manera V, Abrahams S, Ag L, et al. Recommendations for the Nonpharmacological Treatment of Apathy in Brain Disorders A R T I C L E I N F O. *Am J Geriatr Psychiatry*. 2020;28:410-420. doi:10.1016/j.jagp.2019.07.014

38. Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S, Lanctôt KL. Pharmacological interventions for apathy in Alzheimer's disease. *Cochrane database Syst Rev*. 2018;5(5). doi:10.1002/14651858.CD012197.PUB2

39. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. *Mov Disord*. 2019;34(2):180-198. doi:10.1002/MDS.27602

40. Kos C, van Tol MJ, Marsman JBC, Knegtering H, Aleman A. Neural correlates of apathy in patients with neurodegenerative disorders, acquired brain injury, and psychiatric disorders. *Neurosci Biobehav Rev*. 2016;69:381-401. doi:10.1016/J.NEUBIOREV.2016.08.012

41. Tay J, Tuladhar AM, Hollocks MJ, et al. Apathy is associated with large-scale white matter network disruption in small vessel disease. *Neurology*. 2019;92(11):E1157-E1167. doi:10.1212/WNL.0000000000007095

42. Pessiglione M, Vinckier F, Bouret S, Daunizeau J, Le Bouc R. Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. *Brain*. 2018;141(3):629-650. doi:10.1093/BRAIN/AWX278

43. Lisiecka-Ford. DM, Tozer DJ, Morris RG, Lawrence AJ, Barrick TR, Markus HS. Involvement of the reward network is associated with apathy in cerebral small vessel disease. *J Affect Disord*. 2018;232:116-121. doi:10.1016/J.JAD.2018.02.006

44. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: A clinical review. *Neurology*. 2019;92(24):1146-1156. doi:10.1212/WNL.0000000000007654

45. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. *Stroke Vasc Neurol*. 2016;1(3):83-92. doi:10.1136/SVN-2016-000035

46. Ligthart SA, Richard E, Fransen NL, et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69(6):636-642. doi:10.1001/archgenpsychiatry.2011.1858

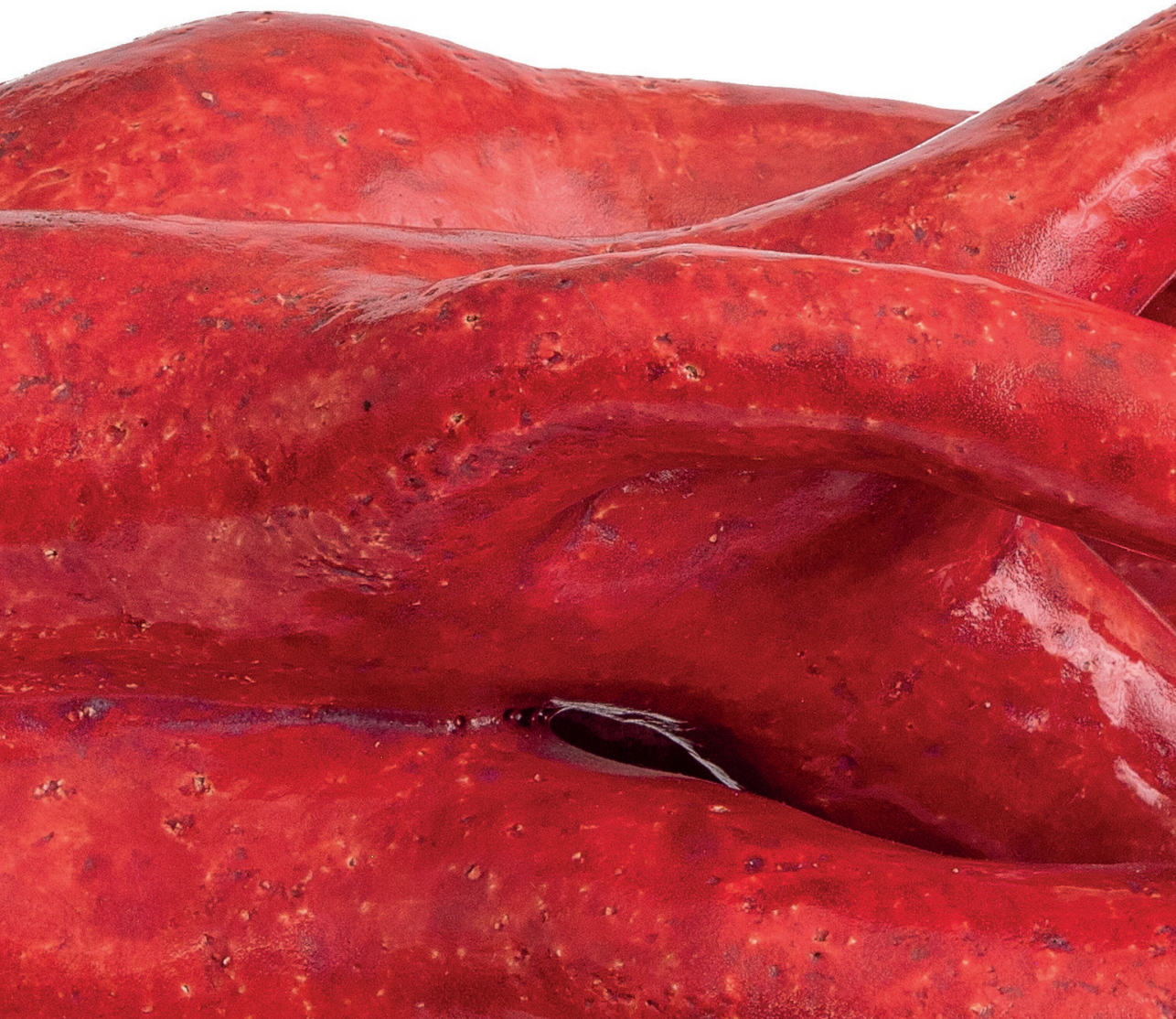
47. Marijnissen RM, Bus BAA, Schoevers RA, et al. Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry*. 2014;22(8):801-810. doi:10.1016/j.jagp.2013.01.001

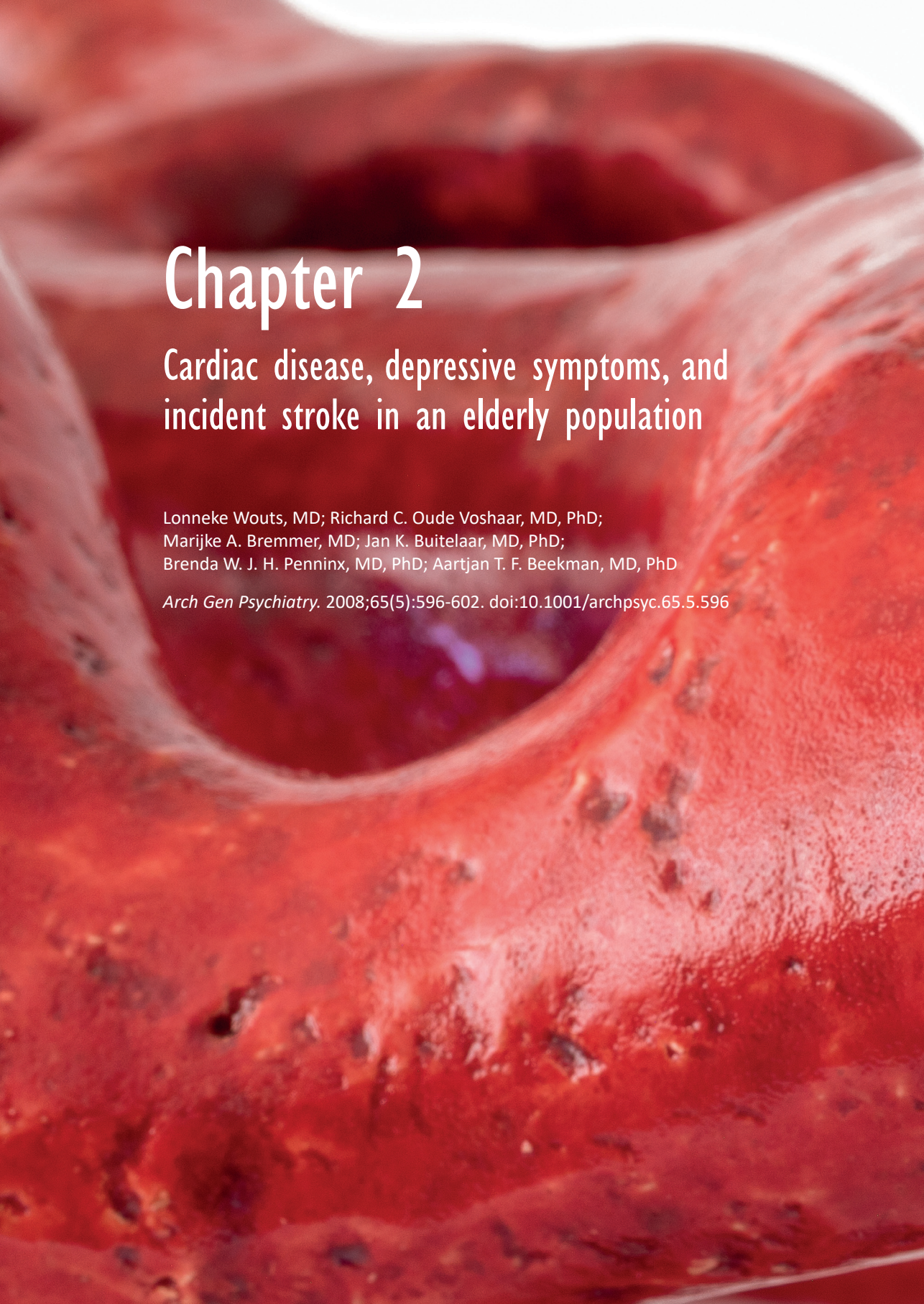
48. Wouts L, Kessel M van, Beekman ATF, Marijnissen RM, Voshaar RCO. Empirical support for the vascular apathy hypothesis: A structured review. *Int J Geriatr Psychiatry*. 2020;35(1):3-11. doi:10.1002/GPS.5217

49. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22(7):613-626. doi:10.1002/GPS.1723

50. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37(6):1583-1633. doi:10.1161/01.STR.0000223048.70103.F1

# Part I





# Chapter 2

## Cardiac disease, depressive symptoms, and incident stroke in an elderly population

Lonneke Wouts, MD; Richard C. Oude Voshaar, MD, PhD;
Marijke A. Bremmer, MD; Jan K. Buitelaar, MD, PhD;
Brenda W. J. H. Penninx, MD, PhD; Aartjan T. F. Beekman, MD, PhD

*Arch Gen Psychiatry.* 2008;65(5):596-602. doi:10.1001/archpsyc.65.5.596

# Abstract

## Context

Previous research suggests that depression is a risk factor for stroke. However, the reliability of much research is limited by the lack of documentation on the presence of preexistent cardiovascular disease and by the use of limited measures of depression or stroke.

## Objectives

To test the hypotheses that (1) clinically relevant depressive symptoms are an independent risk factor of incident stroke in cardiac and noncardiac patients and (2) more chronic and severe depressive symptoms are associated with incident stroke.

## Design

A cohort of elderly Dutch people (aged ≥ 55 years) was followed up for 9 years in the Longitudinal Aging Study Amsterdam (baseline measurements were taken in 1992 or 1993, and the study concluded in 2001 or 2002, respectively).

## Setting

General community.

## Participants

Randomly selected population-based sample (N = 2965) without a history of stroke.

## Main Outcome Measures

The study end point was a first stroke (nonfatal or fatal). Depression was measured using the National Institute of Mental Health Diagnostic Interview Schedule and the Center for Epidemiological Studies–Depression Scale. Multivariate Cox proportional hazards regression analyses of stroke incidence were performed. The association of the chronicity and severity of depressive symptoms was studied in extended models with time-dependent variables.

## Results

The sample's mean (SD) age was 70.5 (8.7) years, 52.1% were women, and the mean (SD) follow-up was 7.7 (3.1) years. Inclusion of an interaction between cardiac disease and clinically relevant depressive symptoms improved the model for stroke ($P$ = .03). In participants with preexistent cardiac disease, but not in participants without cardiac disease, clinically relevant depressive symptoms at baseline (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.17-4.09) and the severity (range, 0-60; HR, 1.08; 95% CI, 1.02-1.13) and chronicity (HR, 3.51; 95% CI, 1.13-10.93) of symptoms during follow-up were associated with stroke.

## Conclusions

Preexistent cardiac disease moderates the association between depressive symptoms and incident stroke. In cardiac patients, baseline depressive symptoms and both the severity and chronicity of symptoms during follow-up are associated with incident stroke.

# Introduction

Depression is highly prevalent among elderly individuals, with a reported prevalence in the community of 1.8% for major depression, 9.8% for minor depression, and 13.5% for clinically relevant depressive symptoms (CRDSs)[1]. Although cross-sectional studies[2] [3]. have shown depression to be associated with poor health, functional impairment, decreased quality of life, and greater use of health services, prospective studies[4] have shown depression and depressive symptoms to be independent determinants of mortality. Recently, myocardial infarction was shown to be a mediator of the higher mortality of depressed individuals[5] [6]. The biological pathways hypothesized to link depression with cardiovascular disease include sympathetic nervous system activation, dysregulation of the hypothalamic-pituitary-adrenocortical axis, platelet aggregation dysfunction, and inflammation[7] [8].

Studies investigating whether depression is also a risk factor for the development of cerebrovascular events have yielded mixed results. The recent consensus guideline of the American Heart Association and the American Stroke Association for the prevention of cerebrovascular events does not mention depression as a possible risk factor for stroke[9]. In a recent meta-analysis,[5] the pooled relative risk of stroke in those with a depressed mood was 1.4 (range, 1.2-1.8), but this estimated risk was influenced by the methodologic shortcomings and heterogeneity of the studies included. In particular, most of the early studies used limited measures of depression, with only 2 using the *DSM-IV* to diagnose depression. The first of these studies used self-reported data on the occurrence of stroke, and the second used physician-reported *ICD-10*–classified cardiovascular disease[10] [11]. Neither study documented the chronicity and severity of depression. Another source of heterogeneity in studies of the relationship between depressive symptoms and stroke is the possible moderating effect of cardiac disease. Because cardiac disease is an important predictor of stroke, stratifying by cardiac disease divides the population into low- and high-risk populations. If one assumes that the pathophysiologic mechanisms are comparable to those leading to cardiovascular disease in depressed individuals, depression in cardiac patients could aggravate the existing atherosclerotic disease, ultimately leading to stroke. Furthermore, the prevalence and incidence of depression would be expected to be higher in cardiac patients based on the vascular depression hypothesis, which states that subclinical underlying cerebrovascular disease may cause depression[12] [13] [14] [15] [16]. According to this hypothesis, underlying atherosclerotic disease could give rise to both stroke and depression in cardiac patients. Bearing in mind these sources of heterogeneity in earlier studies, we investigated whether the presence, severity, and chronicity of depressive symptoms and major depressive disorder (MDD) are independently associated with incident stroke in elderly patients with or without cardiac disease during a 9-year follow-up.

# Methods

## Study design and population

This study was conducted within the Longitudinal Aging Study Amsterdam (LASA), which is a prospective cohort study of Dutch people aged 55 to 85 years. The LASA started in 1992, and its methods have been described in detail elsewhere [17] [18]. The general aim of LASA was to study the autonomy and well-being of an aging population. A randomly selected age- and sex-stratified sample (according to expected mortality figures) was drawn from the population registers of 11 municipalities in the Netherlands. The reason for this relative oversampling of older old people (both men and women) and elderly men was to compensate for an anticipated higher unavailability for follow-up among physically frail people. The initial response rate was 62.3%, and nonresponse was associated with age, sex, and urbanicity. The sample first took part in the cross-sectional NESTOR–living arrangements and social networks study [19] and was later interviewed and followed up every 3 years in LASA; 81.7% of the NESTOR–living arrangements and social networks study population participated in LASA, with nonresponse being related to age but not to sex. All interviews were recorded for quality control purposes. All LASA participants without a history of stroke at the baseline measurement were eligible for inclusion (n = 3018).

Participants in whom depressive symptoms (51 [1.6%]) or stroke (2 [0.06%]) were not evaluated at baseline were excluded. The remaining 2965 individuals participated in this study of the association among depressive symptoms, CRDSs, or MDD at baseline and incident stroke in patients with or without cardiac disease at baseline. The mean (SD) follow-up was 7.7 (3.1) years; participants were assessed at baseline and every 3 years. For the extended Cox proportional hazards regression analyses, we required the availability of a baseline and at least 1 follow-up assessment of depression. In total, 412 participants (13.9%) were excluded because they had died or had a stroke before the first follow-up interview, and 328 participants (11.1%) were excluded because they never had a follow-up assessment of depressive symptoms. Unavailability for follow-up of depressive symptoms was associated with an older age, a lower score on the Mini-Mental State Examination (MMSE), more functional limitations, and cardiac disease ($P < .001$ for all). The mean (SD) follow-up for the remaining 2225 participants was 9.1 (1.7) years, with a mean (SD) number of 3.4 (0.8) measurements of depressive symptoms.

## Measurements

### Stroke Morbidity and Mortality

The study end point was the first occurrence of stroke (fatal or nonfatal). Nonfatal strokes were established based on self-report during the 3-yearly interviews and information obtained from general practitioners (GPs) in response to questionnaires sent in 1992-1993, 1995-1996, and 2000-2001. The GPs were asked whether a participant had ever been diagnosed as having a cerebrovascular accident, the year in which it occurred, and whether a specialist had confirmed the diagnosis. Previous research in LASA had shown

such self-reported information to be moderately accurate (concordance with GP: κ = 0.56; 95% confidence interval [CI], 0.48-0.64) [20]. Therefore, we considered a stroke to have occurred if the self-reported and GP information were consistent or if a cardiac specialist confirmed the GP diagnosis of stroke. Death due to stroke was established based on death certificates registered by the Netherlands Central Bureau of Statistics. Death certificates of deceased participants were 100% complete. Stroke was defined as *ICD-9* codes 431, 433, 434, and 436 and *ICD-10* codes I-61, I-63, and I-64. The event was timed as occurring in the year halfway between the 3-yearly assessments for nonfatal strokes and as the year of death for fatal strokes.



### Depression

Depressive symptoms were measured using the Center for Epidemiological Studies–Depression Scale (CES-D). This is a widely used instrument to measure depressive symptoms in the community [21]. In LASA, the traditional cutoff of the CES-D of 16 or greater had a sensitivity of 100% and a specificity of 88% for MDD [22]. Major depressive disorder was diagnosed using the National Institute of Mental Health Diagnostic Interview Schedule (DIS) [23]. Subthreshold depressive disorder (SDD) was diagnosed if a study participant scored 16 or higher on the CES-D but did not meet *DSM-III* diagnostic criteria for MDD on the DIS. The SDD category included 107 respondents with a CES-D score of 16 or higher but no available DIS diagnosis. We use the term *CRDSs* were refer to the broad category of MDD or SDD, and we use the term *depressive symptoms* to refer to the score on the CES-D (range, 0-60).

The DIS and CES-D were completed every 3 years, which made it possible to estimate the mean severity of depressive symptoms and the chronicity of CRDSs and MDD during the follow-up. The mean severity of depressive symptoms was defined as the mean CES-D score of all observations until the year of the first stroke or censoring divided by the total number of observations in this interval. The chronicity of MDD was defined as the total number of observations of MDD until the year of the first stroke (or censoring) divided by the total number of observations in this interval. The chronicity of CRDSs was the total number of observations of an MDD or a score on the CES-D of 16 or higher until the year of the first stroke (or censoring) divided by the total number of observations in this interval.

### Cardiac Disease

Cardiac disease was defined as myocardial infarction, congestive heart failure, angina pectoris, or cardiac arrhythmia and established at baseline using an algorithm used earlier in LASA[6]. This algorithm uses 3 sources of information: self-reported, medication, and GP information. We considered only 1 confirmative source necessary for diagnosis because self-reported cardiac disease is sufficiently accurate in LASA (concordance with GP: κ = 0.69; 95% CI, 0.65-0.73) [20]. We used a broad definition of cardiac disease because although it could lead to a type II error (overcorrection), the use of a more restricted definition could lead to a type I error (undercorrection), and we preferred to use the broader category.

### Confounders

Sociodemographic variables (sex and age), general health-related variables (functional limitations and cognitive impairments), and important stroke risk factors (diabetes mellitus, smoking, hypertension, and obesity) were included in the analyses as potential confounders. The number of functional limitations was scored with a 3-item questionnaire [24] as none, 1, or 2 or more. Cognitive impairments were measured with the MMSE [25]. A history of diabetes mellitus was considered present if reported by the respondent, if the person used antidiabetic agents, or if a GP confirmed the diagnosis. The variable smoking included current smoking. Blood pressure was measured every 3 years, preferably from the arm but otherwise from the fingertip. Hypertension was categorized into stage 1 hypertension (a mean systolic blood pressure of 140-159 mm Hg or a mean diastolic blood pressure of 90-99 mm Hg) and stage 2 hypertension (a mean systolic blood pressure of ≥ 160 mm Hg or a mean diastolic blood pressure of ≥ 100 mm Hg) [26]. Obesity was defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or greater [27]. Antidepressant use was established by asking about the use of medication and by visually checking all of the participants' medications at each 3-yearly assessment.

### Statistical analyses

All primary variables and covariates were checked for normality, collinearity, and proportionality of hazards. Missing data for covariates were restored by imputation of the most reported value, and the results for analyses with or without imputed data were checked for differences [28]. Baseline characteristics for participants with or without depressive symptoms were compared using $\chi^2$ and *t* tests. Univariate Cox proportional hazards analyses of first strokes were conducted for primary and secondary variables. Models of stroke incidence, which included interaction terms of depression variables (depressive symptoms, CRDSs, and MDD) by cardiac disease status, were tested by multivariate Cox proportional hazard regression analyses. Subsequently, the sample was stratified for cardiac disease, and the relationship between depression variables and incident stroke was examined by multivariate Cox proportional hazard regression analysis. We used extended Cox proportional hazard models to examine the association between the severity of depressive symptoms or the chronicity of CRDSs or MDD and incident stroke, with these depression variables and possible confounders as time-dependent variables [29].

## Results

### Baseline characteristics

The mean (SD) age of the 2965 elderly study participants (52.1% female) was 70.5 (8.7) years, and 39.6% had 1 or more functional limitations (Table 1). At baseline, 58 (2.0%) had MDD and 372 (12.5%) had SDD. Myocardial infarction was reported in 285 (9.6%), congestive heart failure in 256 (8.7%), angina pectoris in 283 (9.5%), and cardiac arrhythmia in 132 (4.4%). The CRDSs at baseline were associated with older age ($P < .001$), female sex ($P < .001$), more functional limitations ($P < .001$), poorer performance on the MMSE ($P < .001$), smoking ($P = .04$), diabetes mellitus ($P = .03$), and cardiac disease ($P < .001$).

*Table 1. Baseline Characteristics*

| Characteristic | Value[A] |
|---|---|
| Age, mean (SD), y | 70.5 ( 8.7) |
| MMSE score, mean (SD)[B] | 27.0 (2.9) |
| MDD | 58 (2.0) |
| CRDS | 430 (14.5) |
| Women | 1546 (52.1) |
| Functional limitations | |
| ≥1 | 1173 (39.6) |
| Smoking | 648 (21.9) |
| Hypertension | |
| stage 1 or 2 | 623 (21.0) |
| Cardiac disease | 611 (20.6) |
| Diabetes mellitus | 358 (12.1) |
| Obesity | 457 (15.4) |

Abbreviations: CRDSs, clinically relevant depressive symptoms, MDD, major depressive disorder, MMSE, Mini-Mental State Examination.

A Data are presented as number (percentage) of participants (N=2965) unless otherwise indicated.

B The range was from 0 to 30.

The overall rate of stroke was 7.7 per 1000 person-years: the rate of first nonfatal stroke was 2.8 per 1000 person-years, and the rate of fatal stroke was 4.9 per 1000 person-years. The rate of incident stroke was higher, but not significantly so, among participants with CRDSs at baseline ($P$ = .10), as shown in Table 2. On univariate analysis, cardiac disease at baseline ($P$ < .001), older age ($P$ < .001), poorer MMSE performance ($P$ < .01), more functional limitations ($P$ < .01), diabetes mellitus ($P$ < .001), and hypertension ($P$ < .001) were associated with a higher incidence of stroke. The use of antidepressants (49 participants [1.7%]) was not associated with incident stroke (hazard ratio [HR], 0.35; 95% CI, 0.05-2.52; $P$ = .30).

*Table 2. Stroke Rates and Univariate Cox Regression on Incident Stroke*

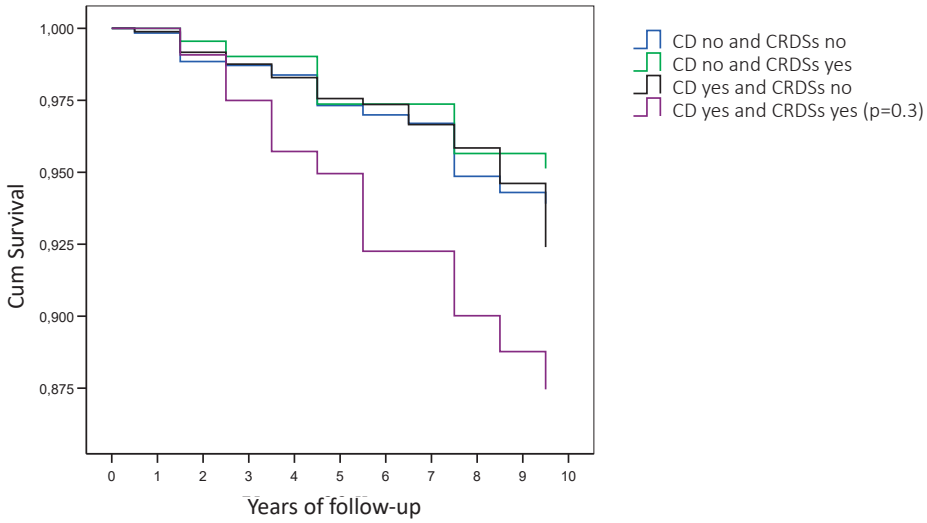
| Variable | | No. of Strokes per 1000 Person-years | Wald statistic | HR (95% CI) | P value |
|---|---|---|---|---|---|
| CRDS | no | 7.4 | | | |
| | yes | 10.11 | 2.645 | 1.39 (0.94-2.1) | .10 |
| Cardiac disease | no | 6.7 | | | |
| | yes | 11.9 | 11.91 | 1.78 (1.28-2.47) | <.001 |

*Abbreviations*: CI, confidence interval; CRDS, clinically relevant depressive symptoms; HR, hazard ratio

## Interaction between cardiac disease and depressive symptoms

Fully corrected survival functions for incident stroke, stratified for cardiac disease status and the presence of CRDSs, are presented in the Figure. The hazard for incident stroke was higher in those with cardiac disease and CRDSs compared with those with cardiac disease but without CRDSs. Multivariate Cox proportional hazards regression demonstrated that inclusion of the interaction term CRDS × cardiac disease (HR, 2.46; 95% CI, 1.09-5.56; *P* = .03) significantly improved the model for incident stroke ($\chi^2$ = 4.7, *P* = .03), as did inclusion of the interaction term depressive symptoms × cardiac disease (HR, 1.06; 95% CI, 1.01-1.11; *P* = .01). Other potentially relevant interaction terms, such as depressive symptoms × diabetes mellitus (*P* = .65), depressive symptoms × stage 1 hypertension (*P* = .69), depressive symptoms × stage 2 hypertension (*P* = .93), and depressive symptoms × smoking (*P* = .85), were not significantly related to incident stroke

*Figure 1. Survival Function (Cox regression) for Incident Stroke at Means of Covariates. CD indicates cardiac disease; CRDSs, clinically relevant depressive symptoms*




*Abbreviations*: CRDS, clinically relevant depressive symptoms; CD, cardiac disease

## Depressive symptoms and incident stroke in patients with and without cardiac disease

Stratification of the sample into those with or without cardiac disease at baseline showed that in patients with cardiac disease the presence of CRDSs at baseline was associated with a higher incidence of stroke even after correction for possible confounders (HR, 2.18; 95% CI, 1.17-4.09; *P* = .02) (Table 3).

The extended multivariate Cox proportional hazards regression model for first stroke included time-dependent depression variables (the mean severity of depressive symptoms, the chronicity of CRDSs, and the chronicity of MDD), possible confounders

measured at baseline, and changes in hypertension or functional limitations during the follow-up period. The chronicity of CRDSs during follow-up was an independent predictor of incident stroke (HR, 3.51; 95% CI, 1.13-10.93; *P* = .03). The chronicity of MDD was not significantly associated with incident stroke (HR, 5.59; 95% CI, 0.77-40.56; *P* = .09). In addition, the mean severity of depressive symptoms during follow-up was significantly associated with an incident stroke (HR, 1.08; 95% CI, 1.02-1.13; *P* = .005). Results were similar for men and women, and correction for cardiac medication did not significantly influence the associations found.

The CRDSs at baseline were not significantly associated with incident stroke in patients without cardiac disease at baseline (Table 3) and neither were the chronicity of CRDSs nor the mean severity of symptoms during follow-up.



*Table 3. Multivariate Cox Regression on Incident Stroke after Stratification for Cardiac Disease*

| | No cardiac disease (n=2354) | | | Cardiac disease (n=611) | | |
|---|---|---|---|---|---|---|
| | **Wald** | **HR (95 %-CI)** | **P-level** | **Wald** | **HR (95 % CI)** | **P-level** |
| **Baseline variables[A]** | | | | | | |
| MDD | 0.64 | 0.44 (0.06-3.22) | .42 | 1.70 | 2.66 (0.61-11.56) | .19 |
| CRDS | 1.15 | 0.73 (0.41-1.30) | .28 | 5.95 | 2.18 (1.17-4.09) | .02 |
| Depressive symptoms (continuous) | 0.90 | 0.99 (0.96-1.01) | .34 | 8.98 | 1.05 (1.02-1.08) | .003 |
| **Time-dependent variables[B]** | | | | | | |
| Chronicity of MDD | 0.42 | 0.39 (0.02-6.86) | .52 | 2.90 | 5.59 (0.77-40.56) | .09 |
| Chronicity of CRDS | 0.02 | 0.94 (0.38-2.31) | .90 | 4.69 | 3.51 (1.13-10.93) | .03 |
| Mean symptom severity (range, 0-60) | 0.64 | 0.98 (0.94-1.03) | .42 | 7.75 | 1.08 (1.02-1.13) | .005 |

*Abbreviations*: CI, confidence interval; CRDSs, clinically relevant depressive symptoms; HR, hazard ratio; MDD, major depressive disorder

[A] Corrected for: age, sex, Mini-Mental State Examination, smoking, functional limitations, hypertension, diabetes mellitus, and obesity.

[B] Corrected for: age, sex, Mini-Mental State Examination, smoking, diabetes mellitus, obesity, functional limitations, and hypertension (baseline) and for a change in functional limitations or hypertension during follow-up (time-dependent).

## Comment

This study shows that cardiac disease moderates the association between CRDSs and incident stroke. In cardiac patients, there seemed to be a dose-response effect in that both the severity and the chronicity of depressive symptoms during follow-up were predictors of incident stroke. This relationship was not observed in patients without cardiac disease at baseline.

Our findings are in line with previous research of the relationship between depressive symptoms and the incidence of stroke in populations with a high cardiovascular risk, such as patients with hypertension or diabetes mellitus [30] [31] [32], and offer an explanation for negative results. They are also consistent with previous studies [12] [33] [34] reporting a poorer cardiac prognosis and an increased mortality among cardiac patients with depression. Our study shows that the cerebrovascular prognosis of cardiac patients with depressive symptoms is worse, as is the cardiac prognosis, and this may be a factor underlying the higher mortality seen in depressed cardiac patients.
Nevertheless, these findings have some limitations. First, stroke was not confirmed by neuroimaging and, thus, no distinction was made between ischemic and hemorrhagic stroke. Pathophysiologically, depression would be expected to be primarily associated with ischemic stroke. Misclassification due to overreporting of stroke is probably not a major issue because self-reported stroke had to be confirmed by a GP or a specialist. Although there was selective dropout, with the more frail individuals being more likely to have missing data on depression during follow-up, this would tend to lead to a conservative estimate of the relationship between depressive symptoms and incident stroke. The relatively few participants with an MDD at baseline (n = 58) limited the power to find associations between MDD and stroke. However, the use of a broader category of CRDSs, which included MDD and SDD, is in line with research showing that subsyndromal depressive states form a continuum with major depression in elderly populations [35] [36] [37]. Furthermore, the strongest results were found when depressive symptoms were used as a continuous measure (based on the CES-D), and the results for time-dependent analysis of an association between MDD and stroke in cardiac patients pointed in the same direction. Last, we did not fully control for the severity of cardiac disease because of the lack of electrocardiographic or ultrasonographic information [12].

As strong points, we used a clinical diagnosis of depression in combination with a valid measurement of depressive symptoms and required confirmation of self-reported stroke by the patients' GPs, a method that has been validated in LASA,[20] or by information obtained from the death certificate. We also assessed depressive disorders and symptoms, functional limitations, and blood pressure during follow-up, which enabled us to use adjusted extended Cox proportional hazards models with time-dependent variables. These extended models are probably more realistic because depression has a fluctuating course, and these models incorporate all available information about depression and depressive symptoms. We also distinguished between participants with and without cardiac disease at baseline, which enabled us to establish that cardiac disease moderates the relationship between stroke and depressive symptoms.

To understand how cardiac disease moderates the association between depression and stroke morbidity and mortality, we initially have to consider why depression is associated with incident stroke in cardiac patients. Depression could aggravate atherosclerosis and in this way worsen the prognosis of cardiac patients, which could explain the dose-response effect that we found. Suggested pathways by which depression could specifically affect the vascular system of cardiac patients are a diminished heart rate variability, altered platelet responses,[8] more arrhythmia in depressed patients with premature ventricular

contractions,[38] as well as behavioral pathways, such as poorer compliance with cardiac treatment and a less healthy lifestyle [39]. At the same time, the vascular depression hypothesis suggests that subclinical underlying cerebrovascular disease can cause depression in cardiac patients [13]. The relationship between depression and vascular diseases seems to be reciprocal [40 41]. This reciprocal relationship could be synergistic in cardiac patients but not in patients without cardiac disease. This would explain the interaction between cardiac disease and depression found in our study.

An alternative explanation for our findings is that depressive symptoms are an indicator of a poor prognosis in cardiac patients because the number of depressive symptoms is (partly) associated with the severity of underlying cardiovascular disease [42]. We chose to use the CES-D to score depressive symptoms because, when LASA was designed, studies showed that the overlap with physical illness was limited [43 44]. A more recent study [45] of patients undergoing cardiac surgery showed that the CES-D detected change after this intervention, not only shortly after surgery but also later during follow-up, which suggests that depressive symptoms, as measured with the CES-D, benefit from an improvement in cardiovascular status. Moreover, trials of antidepressants in depressed patients after myocardial infarction do not consistently report less long-term depression or a better cardiac prognosis, which suggests that depressive symptoms may in part be due to the severity of the underlying cardiac disease [46 47 48 49].

In conclusion, cardiac disease moderates the association between CRDSs and incident stroke. This moderating effect of cardiac disease could be explained not only by a synergistic effect of the reciprocal mechanisms between vascular disease and depression but also by depressive symptoms being an indicator of the severity of underlying cardiac disease. Both explanations deserve more attention in further research because they have implications for targeting effective interventions. At least, depression in cardiac patients seems to be an indicator of a poorer prognosis to some extent because of the higher incidence of stroke among these patients, as this study showed.

**Funding/Support:** This study is based on data collected in the context of LASA, which is largely funded by the Dutch Ministry of Health, Welfare and Sports.

**Additional Contributions:** T. Feuth, MSc, Department of Epidemiology, Biostatistics and High Technology Assessment, and M. Lappenschaar, PhD, Department of Psychiatry, Radboud University Nijmegen Medical Centre, advised us on using extended Cox proportional hazards modeling with time-dependent variables.

## References


1. Beekman ATF, Copeland JRM, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry*. 1999;174(APR.):307-311. doi:10.1192/BJP.174.4.307
2. Herrman H, Patrick DL, Diehr P, et al. Longitudinal investigation of depression outcomes in primary care in six countries: the LIDO Study. Functional status, health service use and treatment of people with depressive symptoms. *Psychol Med*. 2002;32(5):889-902. doi:10.1017/S003329170200586X
3. Katon W, Schulberg H. Epidemiology of depression in primary care. *Gen Hosp Psychiatry*. 1992;14(4):237-247. doi:10.1016/0163-8343(92)90094-Q
4. Penninx BWJH, Geerlings SW, Deeg DJH, Van Eijk JTM, Van Tilburg W, Beekman ATF. Minor and major depression and the risk of death in older persons. *Arch Gen Psychiatry*. 1999;56(10):889-895. doi:10.1001/archpsyc.56.10.889
5. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22(7):613-626. doi:10.1002/GPS.1723
6. Bremmer MA, Hoogendijk WJG, Deeg JH, Schoevers RA. Depression in Older Age Is a Risk Factor for First Ischemic Cardiac Events. *J Geriatr Psychiatry*. 2006;14(6):523.
7. Shimbo D, Chaplin W, Crossman D, Haas D, Davidson KW. Role of depression and inflammation in incident coronary heart disease events. *Am J Cardiol*. 2005;96(7):1016-1021. doi:10.1016/j.amjcard.2005.05.064
8. Musselman DL, Evans DL, Nemeroff CB. The Relationship of Depression to Cardiovascular Disease: Epidemiology, Biology, and Treatment. *Arch Gen Psychiatry*. 1998;55(7):580-592. doi:10.1001/ARCHPSYC.55.7.580
9. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37(6):1583-1633. doi:10.1161/01.STR.0000223048.70103.F1
10. Larson SL, Owens PL, Ford D, Eaton W. Depressive Disorder, Dysthymia, and Risk of Stroke Thirteen-Year Follow-Up From the Baltimore Epidemiologic Catchment Area Study. Published online 2001. Accessed July 13, 2022. http://ahajournals.org
11. Nilsson FM, Kessing L V. Increased risk of developing stroke for patients with major affective disorder--a registry study. *Eur Arch Psychiatry Clin Neurosci*. 2004;254(6):387-391. doi:10.1007/S00406-004-0519-9
12. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27(23):2763-2774. doi:10.1093/EURHEARTJ/EHL338

13. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. "Vascular depression" hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915-922. doi:10.1001/archpsyc.1997.01830220033006

14. Tiemeier H, Van Dijck W, Hofman A, Witteman JCM, Stijnen T, Breteler MMB. Relationship between atherosclerosis and late-life depression: the Rotterdam Study. *Arch Gen Psychiatry*. 2004;61(4):369-376. doi:10.1001/ARCHPSYC.61.4.369

15. De Groot JC, De Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MMB. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry*. 2000;57(11):1071-1076. doi:10.1001/ARCHPSYC.57.11.1071

16. Mast BT, Neufeld S, MacNeill SE, Lichtenberg PA. Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *Am J Geriatr Psychiatry*. 2004;12(1):93-101. Accessed July 13, 2022. https://pubmed-ncbi-nlm-nih-gov.proxy-ub.rug.nl/14729564/

17. Beekman ATF, Deeg DJH, van Tilburg T, Smit JH, Hooijer C, van Tilburg W. Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord*. 1995;36(1-2):65-75. doi:10.1016/0165-0327(95)00061-5

18. Beekman ATF, Geerlings SW, Deeg DJH, et al. The natural history of late-life depression: a 6-year prospective study in the community. *Arch Gen Psychiatry*. 2002;59(7):605-611. doi:10.1001/ARCHPSYC.59.7.605

19. van Tilburg T. Delineation of the social network and differences in network size. In: Knipscheer M, Gierveld J, Tilburg TG van, Dykstra P, eds. *Living Arrangements and Social Networks of Older Adults*. VU University Press; 1995:83-96. http://www.researchgate.net/profile/Theo_Van_Tilburg/publication/227944507_Flow_of_support/links/0046351dbd7574fcee000000.pdf#page=90

20. Kriegsman DMW, Penninx BWJH, Van Eijk JTM, Boeke AJP, Deeg DJH. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol*. 1996;49(12):1407-1417. doi:10.1016/S0895-4356(96)00274-0

21. Radloff LS, Teri L. Use of the Center of Epidemiological Studies-depression scale with older adults. *Clin Gerontol*. 1986;(5):119-136.

22. Beekman ATF, Deeg DJH, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med*. 1997;27(1):231-235. doi:10.1017/S0033291796003510

23. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule: Its History, Characteristics, and Validity. *Arch Gen Psychiatry*. 1981;38(4):381-389. doi:10.1001/archpsyc.1981.01780290015001

24. Van Sonsbeek JLA. Methodological and substantial aspects of the OECD indicator of chronic functional limitations. *Maandber Gezondheid*. 1988;(88):4-17.

25. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6

26. Chobanian A V., Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-2572. doi:10.1001/JAMA.289.19.2560

27. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. *Gastroenterology*. 2007;132(6):2087-2102. doi:10.1053/J.GASTRO.2007.03.052

28. Tabachnick BG, Fidell LS. *Using Multivariate Statistics Title: Using Multivariate Statistics*. 5th ed. Pearson Education; 2005. https://lccn.loc.gov/2017040173

29. Fisher LD, Lin DY. Time-dependent covariates in the cox proportional-hazards regression model. *Annu Rev Public Health*. 1999;20:145-157. doi:10.1146/annurev.publhealth.20.1.145

30. Wassertheil-Smoller S, Applegate WB, Berge K, et al. Change in depression as a precursor of cardiovascular events. SHEP Cooperative Research Group (Systoloc Hypertension in the elderly). *Arch Intern Med*. 1996;156(5):553-561. doi:10.1001/archinte.156.5.553

31. Gump BB, Matthews KA, Eberly LE, Chang YF. Depressive symptoms and mortality in men: results from the Multiple Risk Factor Intervention Trial. *Stroke*. 2005;36(1):98-102. doi:10.1161/01.STR.0000149626.50127.D0

32. Simonsick EM, Wallace RB, Blazer DG, Berkman LF. Depressive symptomatology and hypertension-associated morbidity and mortality in older adults. *Psychosom Med*. 1995;57(5):427-435. doi:10.1097/00006842-199509000-00003

33. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66(6):802-813. doi:10.1097/01.PSY.0000146332.53619.B2

34. Penninx BWJH, Beekman ATF, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001;58(3):221-227. doi:10.1001/ARCHPSYC.58.3.221

35. Hermens MLM, Van Hout HPJ, Terluin B, et al. The prognosis of minor depression in the general population: a systematic review. *Gen Hosp Psychiatry*. 2004;26(6):453-462. doi:10.1016/J.GENHOSPPSYCH.2004.08.006

36. Ormel J, Oldehinkel AJ, Brilman EI. The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *Am J Psychiatry*. 2001;158(6):885-891. doi:10.1176/APPI.AJP.158.6.885

37. Lyness JM, Heo M, Datto CJ, et al. Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. *Ann Intern Med*. 2006;144(7):496-504. doi:10.7326/0003-4819-144-7-200604040-00008

38. Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation*. 1995;91(4):999-1005. doi:10.1161/01.CIR.91.4.999

39. Januzzi JL, Stern TA, Pasternak RC, DeSanctis RW. The influence of anxiety and depression on outcomes of patients with coronary artery disease. *Arch Intern Med*. 2000;160(13):1913-1921. doi:10.1001/ARCHINTE.160.13.1913

40. 40. Camus V, Kraehenbühl H, Preisig M, Büla CJ, Waeber G. Geriatric depression and vascular diseases: what are the links? *J Affect Disord*. 2004;81(1):1-16. doi:10.1016/J.JAD.2003.08.003

41. Baldwin RC. Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. *Int J Geriatr Psychiatry*. 2005;20(1):1-11. doi:10.1002/GPS.1255

42. De Jonge P, Van Melle J. Meta-analysis urges the development of new strategies to treat depression in order to improve cardiac prognosis. *Eur Heart J*. 2007;28(13):1661. doi:10.1093/EURHEARTJ/EHM127

43. Berkman LF, Berkman CS, Kasl S, et al. Depressive symptoms in relation to physical health and functioning in the elderly. *Am J Epidemiol*. 1986;124(3):372-388. doi:10.1093/oxfordjournals.aje.a114408

44. Foelker GA, Shewchuk RM. Somatic complaints and the CES-D. *J Am Geriatr Soc*. 1992;40(3):259-262. doi:10.1111/J.1532-5415.1992.TB02079.X

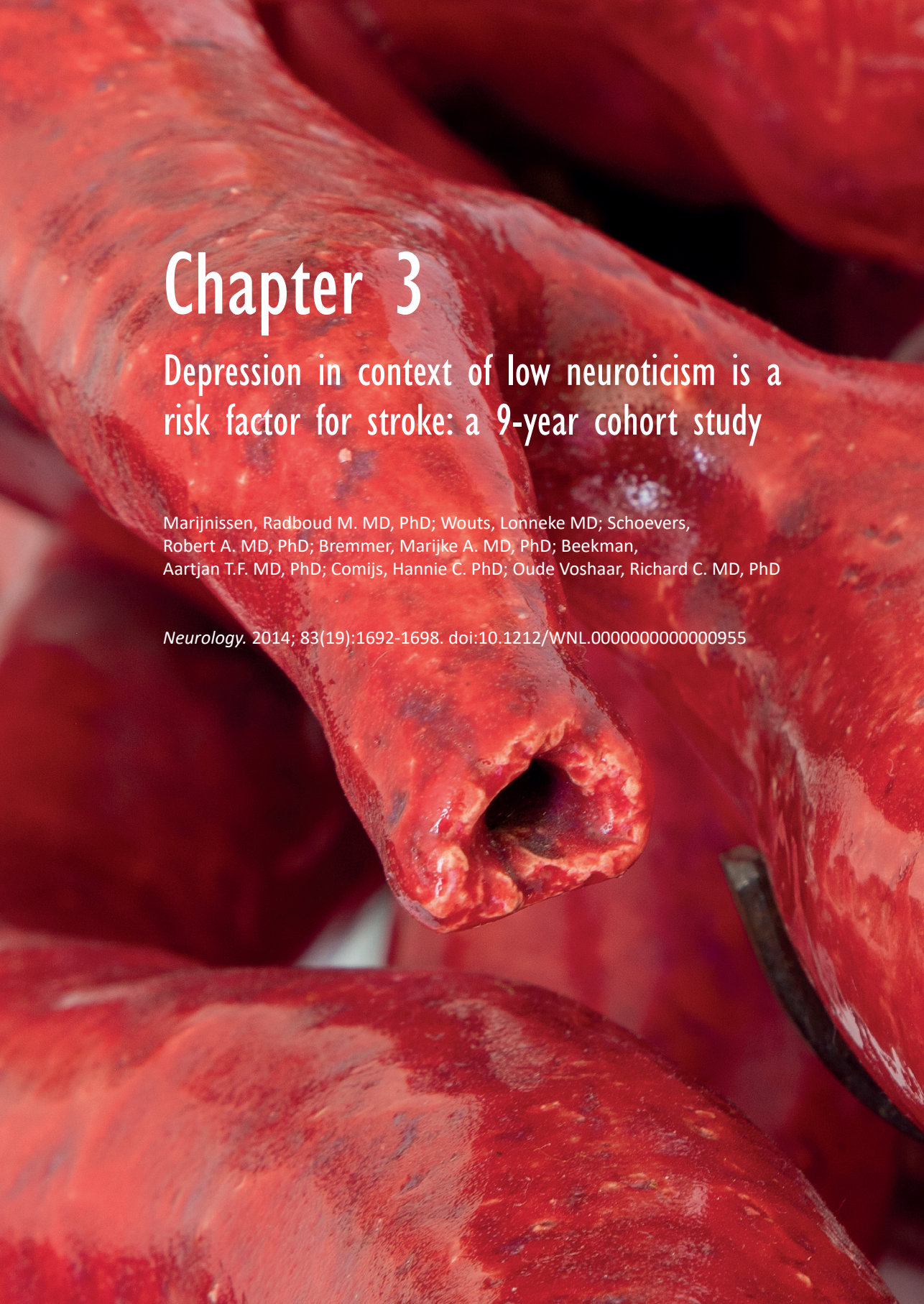
45. Contrada RJ, Boulifard DA, Idler EL, Krause TJ, Labouvie EW. Course of depressive symptoms in patients undergoing heart surgery: confirmatory analysis of the factor pattern and latent mean structure of the Center for Epidemiologic Studies Depression Scale. *Psychosom Med*. 2006;68(6):922-930. doi:10.1097/01.PSY.0000244391.56598.10

46. Van Melle JP, De Jonge P, Honig A, et al. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry*. 2007;190(JUNE):460-466. doi:10.1192/BJP.BP.106.028647

47. Taylor CB, Youngblood ME, Catellier D, et al. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry*. 2005;62(7):792-798. doi:10.1001/ARCHPSYC.62.7.792

48. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003;289(23):3106-3116. doi:10.1001/JAMA.289.23.3106

49. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *J Am Med Assoc*. 2002;288(6):701-709. doi:10.1001/jama.288.6.701



# Chapter 3

## Depression in context of low neuroticism is a risk factor for stroke: a 9-year cohort study

Marijnissen, Radboud M. MD, PhD; Wouts, Lonneke MD; Schoevers, Robert A. MD, PhD; Bremmer, Marijke A. MD, PhD; Beekman, Aartjan T.F. MD, PhD; Comijs, Hannie C. PhD; Oude Voshaar, Richard C. MD, PhD

*Neurology.* 2014; 83(19):1692-1698. doi:10.1212/WNL.0000000000000955

# Abstract

## Objective

Depression predicts stroke; however, meta-analyses show significant heterogeneity. We hypothesize that the risk of depression on incident stroke is conditional upon the relative contribution of vascular disease and of neuroticism in the underlying pathways to depression in a specific patient. We examined whether depression increases stroke in persons with low neuroticism and without preexisting cardiac disease.

## Methods

This was a population-based cohort study with 9-year follow-up (n = 2,050; >=55 years, 52% female). The incidence of stroke was determined by self-report data as well as data from general practitioners and death certificates. Neuroticism was measured using the Dutch Personality Questionnaire and depression using the Center for Epidemiologic Studies-Depression scale. All data were analyzed by Cox proportional hazards regression.

## Results

A total of 117 incident cases of stroke occurred during follow-up. Among persons with a history of cardiac disease (n = 401), depression predicted incident stroke independent of neuroticism level with a hazard ratio (HR) of 1.05 (95% confidence interval [CI] 1.01-1.10) (p = 0.02). In persons without cardiac disease (n = 1,649), depression and neuroticism interacted significantly in predicting incident stroke (p = 0.028). Stratified analyses showed that depression predicted incident stroke in those with low neuroticism, HR 1.05 (95% CI 1.00-1.09) (p = 0.033), but not in those with high neuroticism, HR 1.01 (95% CI 0.96-1.05) (p = 0.82).

## Conclusions

In persons without preexistent cardiac disease, depression is only predictive for future stroke in absence of high neuroticism. This might be explained by the hypothesis that late-life depression in context of low neuroticism is a marker of subclinical vascular disease.

# Introduction

Late-life depression is not only a common and disabling condition in later life, it also predicts the onset of major medical illnesses, such as stroke [1 2 3 4]. Depression is driven by multiple etiologic factors, including personality (such as neuroticism) [5] and vascular factors [2 6 7]. Especially among older people, both of these pathways may act to a certain degree in individual patients. Therefore, the degree to which depression is a predictor of incident stroke might be conditional on the relative weight of vascular disease (vascular depression) and of neuroticism (neurotic depression) as the underlying pathways to depression.

Meta-analyses show that late-life depression is prospectively associated with stroke [3 8]. Nonetheless, the same meta-analyses point to significant heterogeneity across studies [8], that has not been explained properly [8]. Recently, it was found that depression in the oldest-old does not increase stroke risk, but is a risk factor for all-cause mortality [9]. The effects of depression on stroke risk may be due to residual confounding by severity of subclinical vascular disease [10]. Many older persons without a history of ischemic heart disease or stroke have a significant level of vascular pathology in presence of generalized atherosclerosis. Recently, we have shown that the intima-media thickness of the carotid artery, a marker for generalized atherosclerosis, is associated with depressive symptoms, even in the absence of a history of vascular events [11] . This association, however, was confined to the somatic-affective symptoms domain of depression, which may indeed point to overlap between subclinical vascular disease and depression [11]. Interestingly, incident depression after a myocardial infarction also predicted a poorer prognosis of heart disease, whereas recurrent depression as well as depression associated with a high level of neuroticism did not [12 13 14]. These findings fit with the hypothesis that the risk of depression on future vascular events is conditional upon depressive symptoms related to underlying vascular disease and not upon neuroticism-associated depression.

In the Longitudinal Aging Study Amsterdam (LASA), we have shown that depression only predicted incident stroke in older persons with preexisting cardiac disease [4]. A logical explanation would be that in noncardiac patients the contribution of vascular disease burden to depression is minimal and other pathways like high levels of neuroticism may be more important. Nonetheless, this explanation does not fully fit with abovementioned findings that depression is also associated with subclinical vascular disease [11]. The present study, therefore, is an extension of our previous findings in LASA [4] .

We assume that the association between depression and vascular events is confounded by underlying vascular disease in later life and that this may differ for different subtypes of depression (vascular vs neurotic-associated depression). The aim of this study was to examine whether a lower level of neuroticism in older persons with depression without preexisting cardiac disease would be associated with increased risk of stroke in LASA. We a priori hypothesize that vascular depression, defined theoretically by a high etiologic contribution of vascular disease, increases the risk on future strokes, whereas neuroticism-associated depression does not.

# Methods

## Study design and population

This study was performed as part of the LASA. LASA is a prospective cohort study focusing on physical functioning and well-being of an older (>=55 years) population (n = 3,107). LASA started in 1992/1993, with follow-up measurements every 3 years (see references [15] and [16]). For this particular study, 9 years of follow-up data were available. Eligible were those participants without a history of stroke (n = 3,018, 97.1%), allowing us to study incident stroke and availability of baseline data on depressive symptoms (missing for 51 participants) and stroke (missing for 2 participants). Of these 2,965 eligible LASA participants, 915 participants had no data on neuroticism, leaving a final sample of 2,050 participants. The number of missing measurements on neuroticism was high because of the method of measurement: participants were asked to return a self-report questionnaire on neuroticism after being interviewed. Table 1 presents the baseline characteristics for those participants with and without data on neuroticism.

*Table 1. Characteristics of included patients versus those with missing data on neuroticism*

| Characteristic | | Included (n=2050) | Excluded (n=915) | Statistics |
|---|---|---|---|---|
| Age (years) | Mean (SD) | 69.3 (8.5) | 73.2 (8.6) | p<.001 |
| Female sex | n (%) | 1046 (51.0%) | 500 (54.6%) | p=.068 |
| Cognitive functioning (MMSE score) | Mean (SD) | 27.5 (2.3) | 25.9 (3.6) | p<.001 |
| Depressive symptoms (CESD score) | Mean (SD) | 7.4 (7.4) | 8.9 (8.4) | p<.001 |
| One or more functional limitations | n (%) | 728 (35.7%) | 445 (49.3%) | p<.001 |
| Smoking (yes) | n (%) | 477 (24.4%) | 171 (27.7%) | p=.098 |
| Stage 1 or 2 hypertension | n (%) | 479 (24.9%) | 144 (23.6%) | p=.528 |
| Cardiac disease | n (%) | 401 (19.6%) | 210 (23.0%), | p=.035 |
| Diabetes mellitus | n (%) | 224 (10.9%) | 134 (14.7%) | p=.004 |
| Obesity | n (%) | 323 (17.6%) | 134 (21.6%) | p=.024 |
| Use of antidepressants | n (%) | 37 (1.9%) | 12 (1.9%) | p=.946 |
| Incident stroke | n (%) | 117 (5.7%), | 59 (6.4%) | p=.430 |

*Abbrevations*: SD, standard deviation; n, number of participants; MMSE, Mini Mental State Examination; CESD, Center for Epidemiologic Studies Depression scale

## Standard protocol approvals, registrations, and patient consents

All participants of LASA completed an informed consent after oral and written information. The Medical Ethics Committee of the VU University Medical Center approved the study design and procedures.

## Variables of interest

### Stroke morbidity and mortality

Nonfatal stroke was assessed using an algorithm based on the 3-yearly prospective

interviews and general practitioner (GP) information (as in the Netherlands all patients are linked to only 1 GP, who receives all medical information from specialists). Previously, a LASA study showed that self-report information on stroke was reasonably moderately accurate when compared with GP information (concordance: [kappa] = 0.56; 95% confidence interval [CI] 0.48-0.64) and that concordance did not covary with level of depressive symptoms of patients [17]. We considered a stroke to have occurred if self-reported and GP information was consistent or if a medical specialist had confirmed the GP diagnosis of stroke.

Fatal stroke was defined as ICD-9 codes 431, 433, 434, and 436 and ICD-10 codes I-61, I-63, and I-64 on the death certificates registered by the Netherlands Central Bureau of Statistics. These were 100% complete.
The primary outcome, time to stroke, is calculated for nonfatal stroke as the time between baseline and halfway the year for which the stroke has been reported; for fatal stroke, the exact time between baseline and death.



### Depression

Depressive symptoms were measured using the self-report Center for Epidemiologic Studies Center for Epidemiologic Studies-Depression (CES-D) scale. All 20 items refer to the past week and are scored on a 4-point scale (sum score range 0-60). The psychometric properties of the scale are good in an older population and overlap with symptoms of physical illness is minimal [18]. A score of >=16 indicates clinically relevant depressive symptoms [19]. In LASA, the cutoff of 16 or higher had a sensitivity of 100% and a specificity of 88% for major depressive disorder according to DSM-IV criteria [19].

### Neuroticism

Neuroticism is a personality trait that is stable across the lifespan and not affected by physical health status [20]. People with a high level of neuroticism are sensitive to negative stimuli [21], causing emotional instability and negative moods like anxiety, sadness, guilt, hostility, and self-dissatisfaction [20 22]. Neuroticism was measured using the Dutch Personality Questionnaire (DPQ) [23]. Pilot studies before LASA started showed that the original scale of 36 items could be abbreviated without loss of validity or reliability [24 25]. These DPQ items have strong negative relations with the Emotional Stability Scale of the NEO Personality Inventory-Revised [23]. The DPQ asks respondents if statements apply to them; possible answers are yes/do not know/no. Scores range between 0 and 50.

### Cardiac disease

As previously described [4]: “Cardiac disease was defined as myocardial infarction, congestive heart failure, angina pectoris, or cardiac arrhythmia and established at baseline using an algorithm used earlier in LASA [26]. This algorithm uses 3 sources of information: self-reported, medication, and GP information. We considered only 1 confirmative source necessary for diagnosis because self-reported cardiac disease is sufficiently accurate in LASA (concordance with GP: [kappa] = 0.69; 95% CI 0.65-0.73).” [17]

## Potential confounders (covariates)

Age, sex, general health-related variables (functional limitations and cognitive impairments), and established stroke risk factors (smoking, obesity, diabetes mellitus, and hypertension) were considered potential confounders and as such were included in the analyses [18].

Functional limitations were scored as none, 1, or >=2, using a 3-item questionnaire [27]. Cognition was measured with the Mini-Mental State Examination (MMSE) [28]. The variable smoking included current smoking. Obesity was defined as a body mass index of 30 kg/m2 or greater [29]. Diabetes mellitus (yes/no) was based on self-report data, the use of antidiabetic agents, or a GP diagnosis [17]. Blood pressure (mm Hg) was measured with an oscillometric blood pressure monitor (HEM-706; Omron Corporation, Tokyo, Japan) after 5 minutes of rest. Out of the 3 measurements, a mean systolic blood pressure of 140-159 mm Hg or a mean diastolic blood pressure of 90-99 mm Hg was categorized as stage 1 hypertension. A mean systolic blood pressure of >=160 mm Hg or a mean diastolic blood pressure of >=100 mm Hg was categorized as stage 2 hypertension [30]. Antidepressant use was established by visually checking all of the participants' medications during interview at their homes.

## Statistical methods

Differences between groups were explored by calculating descriptive statistics (e.g., means, SDs, and frequencies) and performing t tests for continuous measures with normal distributions, Mann-Whitney U tests for continuous measures with skewed distributions, and [chi]2 tests for categorical variables.

We checked the primary variables for normality, collinearity, and proportionality of hazards. Neuroticism was not normally distributed; therefore we classified respondents as low or high on neuroticism based on the median split (=5) in order to prevent influential outliers from affecting results. We also performed sensitivity analyses by repeating all analyses on the log-transformed continuous neuroticism score.

The predictive effect of depression on incidence of stroke was tested with multiple Cox regression analyses with time to a fatal or nonfatal stroke as the dependent variable and corrected for age, sex, global cognitive functioning (MMSE score), one or more functional limitations, smoking, hypertension (stage 1 or 2), diabetes mellitus, and obesity. Depression was examined both as a continuous measure based on the CES-D total sum score as well as dichotomized (>=16), indicative of clinically relevant depressive symptoms.

We first checked for an interaction between depression and the presence of cardiac disease using Cox proportional hazards regression models with stroke as the dependent variable. In the fully adjusted models, the hazard ratio (HR) for clinically relevant depressive symptoms by cardiac disease status was 4.03 (95% CI 1.22-13.28) (p = 0.022) and HR for

severity of depressive symptoms by cardiac disease status was 1.06 (95% CI 1.01-1.11) (p = 0.032). Therefore, all analyses will be stratified for baseline cardiac disease status.

For the present article, we examined interaction terms between depression and neuroticism on incidence of stroke when stratified for preexisting cardiac disease using multiple Cox regression analyses. In case of significant interactions with neuroticism, results are presented separately for participants with low and high neuroticism scores.

All analyses were conducted in SPSS (Chicago, IL) for Macintosh 2011. We considered p values <0.05 as significant.

# Results

## Baseline characteristics



The mean (SD) age of the 2,050 study participants was 69.3 (8.5) years and 1,046 (51.0%) were women (table 1). At baseline, 261 (12.7%) participants had clinically relevant depressive symptoms, whereas the median neuroticism score was 4.0 (interquartile range 7.0). A total of 117 incident strokes occurred during follow-up, resulting in an overall stroke rate of 7.0 per 1,000 person-years. Table 2 presents the baseline characteristics by cardiac disease status.

*Table 2. Characteristics of included patients by cardiac disease status*

| Characteristic | | No cardiac disease (n=1649) | Cardiac disease (n=410) | Statistics |
|---|---|---|---|---|
| Age (years) | Mean (SD) | 68.6 (8.4) | 72.4 (8.3) | p<.001 |
| Female sex | n (%) | 889 (53.9%) | 157 (39.2%) | p<.001 |
| Cognitive functioning (MMSE score) | Mean (SD) | 27.5 (2.3) | 27.2 (2.4) | p=.007 |
| Depressive symptoms (CESD score) | Mean (SD) | 7.1 (7.2) | 8.9 (8.3) | p<.001 |
| Neuroticism (DPQ score) | median (IQR) | 4.0 (7.0) | 5.0 (9.0) | p=.018 |
| One or more functional limitations | n (%) | 520 (31.7%) | 208 (52.4%) | p<.001 |
| Smoking (yes) | n (%) | 384 (24.6%) | 93 (23.8%) | p=.752 |
| Stage 1 or 2 hypertension | n (%) | 398 (25.8%) | 81 (21.0%) | p=.052 |
| Diabetes mellitus | n (%) | 159 (9.6%) | 65 (16.2%) | p<.001 |
| Obesity | n (%) | 251 (17.0%) | 72 (20.1%) | p=.160 |
| Use of antidepressants | n (%) | 32 (2.0%) | 5 (1.3%) | p=.319 |
| Incident stroke | n (%) | 85 (5.2%) | 32 (8.0%) | p=.029 |

*Abbrevations*: Standard deviation; n, number of participants, MMSE, Mini Mental State Examination; CESD, Center for Epidemiologic Studies Depression scale; DPQ, Dutch Personality Questionnaire; IQR, Interquartile Range

## Results by level of neuroticism

Table 3 shows the effect of depression and neuroticism on the onset of stroke in patients with and without cardiac disease separately. Adjusted for covariates, the interaction term of neuroticism (median split) by depression was only significant in patients without cardiac disease.

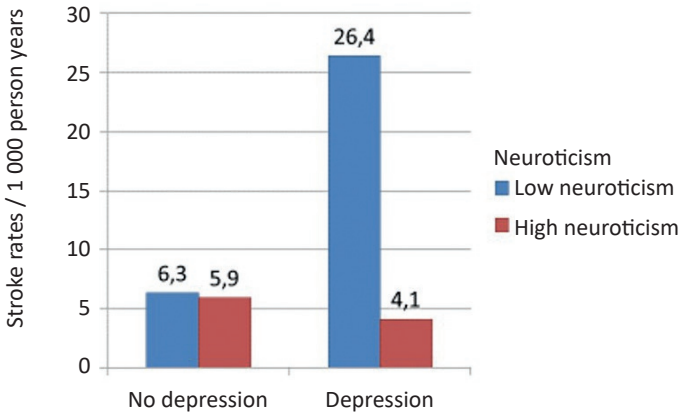
*Table 3. Models for Stroke which include interaction neuroticism (median split) by depression**

| | No cardiac disease | | | Cardiac disease** | | |
|---|---|---|---|---|---|---|
| | **HR** | **[95% CI]** | **p-value** | **HR** | **[95% CI]** | **p-value** |
| *Model 1:* | | | | | | |
| • CESD score | 1.12 | [1.03 – 1.22] | .008 | 0.97 | [0.79 – 1.20] | .776 |
| • Neuroticism | 1.06 | [0.57 – 1.98] | .854 | 0.74 | [0.23 – 2.44] | .625 |
| • CESD by Neuroticism | 0.94 | [0.89 – 0.99] | .028 | 1.05 | [0.94 – 1.17] | .440 |
| *Model 2:* | | | | | | |
| • CESD score ≥16 | 42.6 | [5.23 – 347] | <.001 | 0.37 | [0.01 – 26.3] | .649 |
| • Neuroticism | 0.85 | [0.54 – 1.35 | .484 | 1.04 | [0.43 – 2.48] | .936 |
| • CESD by Neuroticism | 0.12 | [0.03- 0.45] | .002 | 2.60 | [0.27 – 25.2] | .408 |

Adjusted for age, sex, cognitive functioning, smoking, obesity, diabetes mellitus, functional limitations, and hypertension.
*Abbrevations*: CESD, Center for Epidemiologic Studies Depression scale

Removing the interaction term from analyses within those participants with cardiac disease (n = 401) showed that depression predicted incident stroke (HR depressive symptoms = 1.05 [95% CI 1.01-1.10], p = 0.020; HR clinically relevant depressive symptoms = 2.08 [95% CI 0.93-4.63, p = 0.075, respectively]), whereas neuroticism did not (HR 1.06 [95% CI 0.47-2.38], p = 0.88; and HR 1.23 [95% CI 0.57-2.68], p = 0.60, respectively). Neuroticism was not identified as an independent predictor of stroke risk in any of the models (all p values > 0.05).

*Figure 1. Absolute stroke rates per 1,000 person-years by depression and neuroticism status in patients with no cardiac history (n=1,649)*




Stratified analyses by neuroticism status in participants without cardiac disease (n = 1,649) showed that when adjusted for covariates, depression predicted incident stroke in those with low neuroticism (n = 838): HR depressive symptoms = 1.05 (95% CI 1.00-1.09) (p = 0.033) and HR clinically relevant depressive symptoms = 4.53 (95% CI 1.72-11.9) (p = 0.002), respectively, but not in those with high neuroticism (n = 811): HR depressive symptoms = 1.01 (95% CI 0.96-1.05) (p = 0.82) and HR clinically relevant depressive symptoms = 0.78 (95% CI 0.30-2.06) (p = 0.62), respectively. The figure presents the absolute stroke rates per 1,000 person-years by depression and neuroticism status in patients with no cardiac history (n = 1,649).

Stratifying on dichotomized CES-D scores and neuroticism scores (as done in the figure) results in low numbers per group. In the nondepressed group (n = 1,463), 5.2% (42/805) of persons with low neuroticism had an incident stroke, vs 5.0% (33/658) of persons with high neuroticism. In the depressed group (n = 186), 15.2% (5/33) of persons with low neuroticism had an incident stroke, vs 3.3% (5/153) of persons with high neuroticism.
As dichotomized data are more prone to chance findings, we also reanalyzed the data using 10Log transformation of neuroticism and the sum score of the CES-D. These analyses fully supported the results (data not shown).

## Discussion

In older persons without preexistent cardiac disease, depression only predicts the onset of stroke over a 9-year follow-up in case of low neuroticism scores. Although we did not directly measure the level of subclinical vascular disease with imaging techniques, this finding may be explained by the presence of subclinical cardiovascular as well as cerebrovascular disease for the following reasons. Atherosclerosis generally develops over years, with the ultimate outcome of a cardiac or cerebrovascular event [31]. Nonetheless, subclinical vascular disease is also associated with (specific) depressive symptoms [11]. In case atherosclerosis first gives rise to an increased depressive symptom score, depression will emerge as a predictor for stroke in observational cohort studies. How does this theory fit with our results? First, our finding that depression increases the risk for stroke in patients with cardiac disease is in line with the theory that depressive symptoms in this population partly reflect the severity of underlying subclinical vascular disease [5 8]. In people without preexisting cardiac disease, neuroticism may be assumed to be the most important pathway to depression (neurotic depression) [32]. Nonetheless, in this group, several persons have low neuroticism scores that by definition cannot have contributed to their depression. In this group, depressive symptoms may be a sign (or epiphenomenon) of subclinical vascular disease. Indeed, this hypothesis fits with our finding that depression in the presence of low neuroticism scores predicts the onset of stroke in persons without manifest cardiac disease.

The interplay among neuroticism, vascular disease, and depression is complex. Cross-sectional studies show that the association between depression and neuroticism is weaker in patients with vascular disease [32 33]. Prospective studies studying the effect of neuroticism and depression on the incidence of stroke in concert are lacking. Nonetheless, some studies suggest that high levels of neuroticism may increase risk of vascular events. In the Swedish Twin Register, neuroticism predicted the development of coronary heart disease over 25 years of follow-up, but significance was lost after controlling for familial influences [34]. In the UK Health and Lifestyle Survey, neuroticism predicted cardiac mortality, but not death from stroke [35]. In the Chicago Health and Aging Project, a psychosocial composite score including items of neuroticism was associated with an increased risk on stroke over and above the classical vascular risk factors for stroke [36]. As this composite score also included depression, perceived stress, and life dissatisfaction, the net effect of neuroticism remains unknown. It is most likely that neuroticism by itself is not related to vascular health, as was found in our study.

Three limitations should be taken into account. First, there was a selective dropout at baseline, as persons with missing neuroticism scores were more depressed and more vascular comprised. This might have reduced the power of the results in the cardiac subgroup, in which no differential impact of depression by neuroticism status could be demonstrated. Effects for the noncardiac subgroup are difficult to estimate, but most likely, results are conservative.

Second, biological markers of physical diseases have not been measured extensively. Previous articles on LASA, however, have confirmed good validity and high accuracy of our interview and algorithms used to classify the presence or absence of disease states [17 26]. Nonetheless, many patients have asymptomatic atrial fibrillation in later life, which may have underestimated our prevalence of cardiac arrhythmias [37].

Third, the number of participants with a stroke within subgroups was rather low, especially in the subgroup of nondepressed, noncardiac patients. Therefore, confirmation in other samples seems relevant in order to rule out chance findings. Nonetheless, our findings within subgroups categorized by depression (yes/no) and neuroticism (high/low) status were confirmed by analyses using depressive symptoms and neuroticism dimensionally.

Neuroticism and vascular disease are 2 major vulnerability factors in late-life depression [1 22 32]. Patients with depression with high levels of neuroticism are more likely to benefit from classical antidepressant treatment strategies, compared to patients with depression with higher level of vascular disease [38 39]. These latter patients are also at increased risk of future health events like stroke 4 and might benefit from optimizing vascular disease management, including lifestyle intervention like walking or running. Therefore, replication studies as well as randomized controlled studies on the surplus of vascular screening in non-neurotic older patients with depression without known vascular disease are warranted.

The results of our study suggest that in older persons with depression without a history of clinically overt vascular disease, persons with a low level of neuroticism have a higher risk of developing stroke, compared to those with a high level of neuroticism. These results support the idea that neurotic depression is a different type of depression than depression associated with vascular disease. Moreover, late-life depression in the context of low neuroticism might be a marker of vascular depression. This can be explained by subclinical vascular disease, in line with previous findings of an association between measures of generalized atherosclerosis and depressive symptoms in the population [11].

## Glossary

CES-D: Center for Epidemiologic Studies-Depression scale
CI: confidence interval
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition
GP: general practitioner
HR: hazard ratio
ICD: International Classification of Diseases
LASA: Longitudinal Aging Study Amsterdam
MMSE: Mini-Mental State Examination

## References


1. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22(7):613-626. doi:10.1002/GPS.1723
2. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963-974. doi:10.1038/mp.2013.20
3. Valkanova V, Ebmeier KP. Vascular risk factors and depression in later life: a systematic review and meta-analysis. *Biol Psychiatry*. 2013;73(5):406-413. doi:10.1016/J.BIOPSYCH.2012.10.028
4. Wouts L, Voshaar RCO, Bremmer MA, Buitelaar JK, Penninx BWJH, Beekman ATF. Cardiac disease, depressive symptoms, and incident stroke in an elderly population. *Arch Gen Psychiatry*. 2008;65(5):596-602. doi:10.1001/archpsyc.65.5.596
5. Steunenberg B, Beekman ATF, Deeg DJH, Kerkhof AJFM. Personality and the onset of depression in late life. *J Affect Disord*. 2006;92(2-3):243-251. doi:10.1016/J.JAD.2006.02.003
6. Sneed JR, Rindskopf D, Steffens DC, Krishnan KRR, Roose SP. The vascular depression subtype: evidence of internal validity. *Biol Psychiatry*. 2008;64(6):491-497. doi:10.1016/J.BIOPSYCH.2008.03.032
7. Ormel J, De Jonge P. Unipolar depression and the progression of coronary artery disease: toward an integrative model. *Psychother Psychosom*. 2011;80(5):264-274. doi:10.1159/000323165
8. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA*. 2011;306(11):1241-1249. doi:10.1001/JAMA.2011.1282
9. Köhler S, Verhey F, Weyerer S, et al. Depression, non-fatal stroke and all-cause mortality in old age: a prospective cohort study of primary care patients. *J Affect Disord*. 2013;150(1):63-69. doi:10.1016/J.JAD.2013.02.020
10. De Jonge P, Roest AM. Depression and cardiovascular disease: the end of simple models. *Br J Psychiatry*. 2012;201(5):337-338. doi:10.1192/BJP.BP.112.110502
11. Bus BAA, Marijnissen RM, Holewijn S, et al. Depressive symptom clusters are differentially associated with atherosclerotic disease. *Psychol Med*. 2011;41(7):1419-1428. doi:10.1017/S0033291710002151
12. Spijkerman T, De Jonge P, Van Den Brink RHS, et al. Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. *Gen Hosp Psychiatry*. 2005;27(6):411-417. doi:10.1016/J.GENHOSPPSYCH.2005.05.007
13. de Jonge P, van den Brink RHS, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *J Am Coll Cardiol*. 2006;48(11):2204-2208. doi:10.1016/J.JACC.2006.06.077

14. Dickens C, McGowan L, Percival C, et al. New onset depression following myocardial infarction predicts cardiac mortality. *Psychosom Med*. 2008;70(4):450-455. doi:10.1097/PSY.0B013E31816A74DE

15. Beekman ATF, Deeg DJH, van Tilburg T, Smit JH, Hooijer C, van Tilburg W. Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord*. 1995;36(1-2):65-75. doi:10.1016/0165-0327(95)00061-5

16. Beekman ATF, Geerlings SW, Deeg DJH, et al. The natural history of late-life depression: a 6-year prospective study in the community. *Arch Gen Psychiatry*. 2002;59(7):605-611. doi:10.1001/ARCHPSYC.59.7.605

17. Kriegsman DMW, Penninx BWJH, Van Eijk JTM, Boeke AJP, Deeg DJH. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol*. 1996;49(12):1407-1417. doi:10.1016/S0895-4356(96)00274-0

18. Beekman ATF, Deeg DJH, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med*. 1997;27(1):231-235. doi:10.1017/S0033291796003510

19. Berkman LF, Berkman CS, Kasl S, et al. Depressive symptoms in relation to physical health and functioning in the elderly. *Am J Epidemiol*. 1986;124(3):372-388. doi:10.1093/oxfordjournals.aje.a114408

20. Steunenberg B, Beekman ATF, Deeg DJH, Bremmer MA, Kerkhof AJFM. Mastery and neuroticism predict recovery of depression in later life. *Am J Geriatr Psychiatry*. 2007;15(3):234-242. doi:10.1097/01.JGP.0000236595.98623.62

21. Tellegen A. Structures of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In: Tuma AH, Maser JD, eds. *Anxiety and the Anxiety Disorders.* Erlbaum.; 1985:681-706.

22. Watson D, Clark LA. Negative affectivity: the disposition to experience aversive emotional states. *Psychol Bull*. 1984;96(3):465-490. doi:10.1037/0033-2909.96.3.465

23. Luteijn F, Starren J, Van Dijk H. *Herziene Handleiding Bij de NPV (Revised Manual Dutch Personality Questionnaire).* Swets & Zeitlinger; 2000.

24. Smits CHM, Deeg DJH, Bosscher RJ. Well-being and control in older persons: the prediction of well-being from control measures. *Int J Aging Hum Dev*. 1995;40(3):237-251. doi:10.2190/JH5F-2XWH-Y101-7EWF

25. Steunenberg BB. Neuroticism in the elderly. (The utility of the shortened DPQ-scales). *Tijdschr voor Gerontol en Geriatr*. 2003;34(3):118-124.

26. Bremmer MA, Hoogendijk WJG, Deeg JH, Schoevers RA. Depression in Older Age Is a Risk Factor for First Ischemic Cardiac Events. *J Geriatr Psychiatry*. 2006;14(6):523.

27. Van Sonsbeek JLA. Methodological and substantial aspects of the OECD indicator of chronic functional limitations. *Maandber Gezondheid*. 1988;(88):4-17.

28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6

29. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. *Gastroenterology*. 2007;132(6):2087-2102. doi:10.1053/J.GASTRO.2007.03.052

30. Chobanian A V., Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-2572. doi:10.1001/JAMA.289.19.2560

31. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*. 1993;362(6423):801-809. doi:10.1038/362801A0

32. Marijnissen RM, Bus BAA, Schoevers RA, et al. Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry*. 2014;22(8):801-810. doi:10.1016/j.jagp.2013.01.001

33. Wouts L, Janzing JG, Lampe IK, et al. The interaction between cerebrovascular disease and neuroticism in late-life depression: A cross-sectional study. *Int J Geriatr Psychiatry*. 2011;26(7):702-710. doi:10.1002/gps.2584

34. 34. Charles ST, Gatz M, Kato K, Pedersen NL. Physical health 25 years later: the predictive ability of neuroticism. *Health Psychol*. 2008;27(3):369-378. doi:10.1037/0278-6133.27.3.369

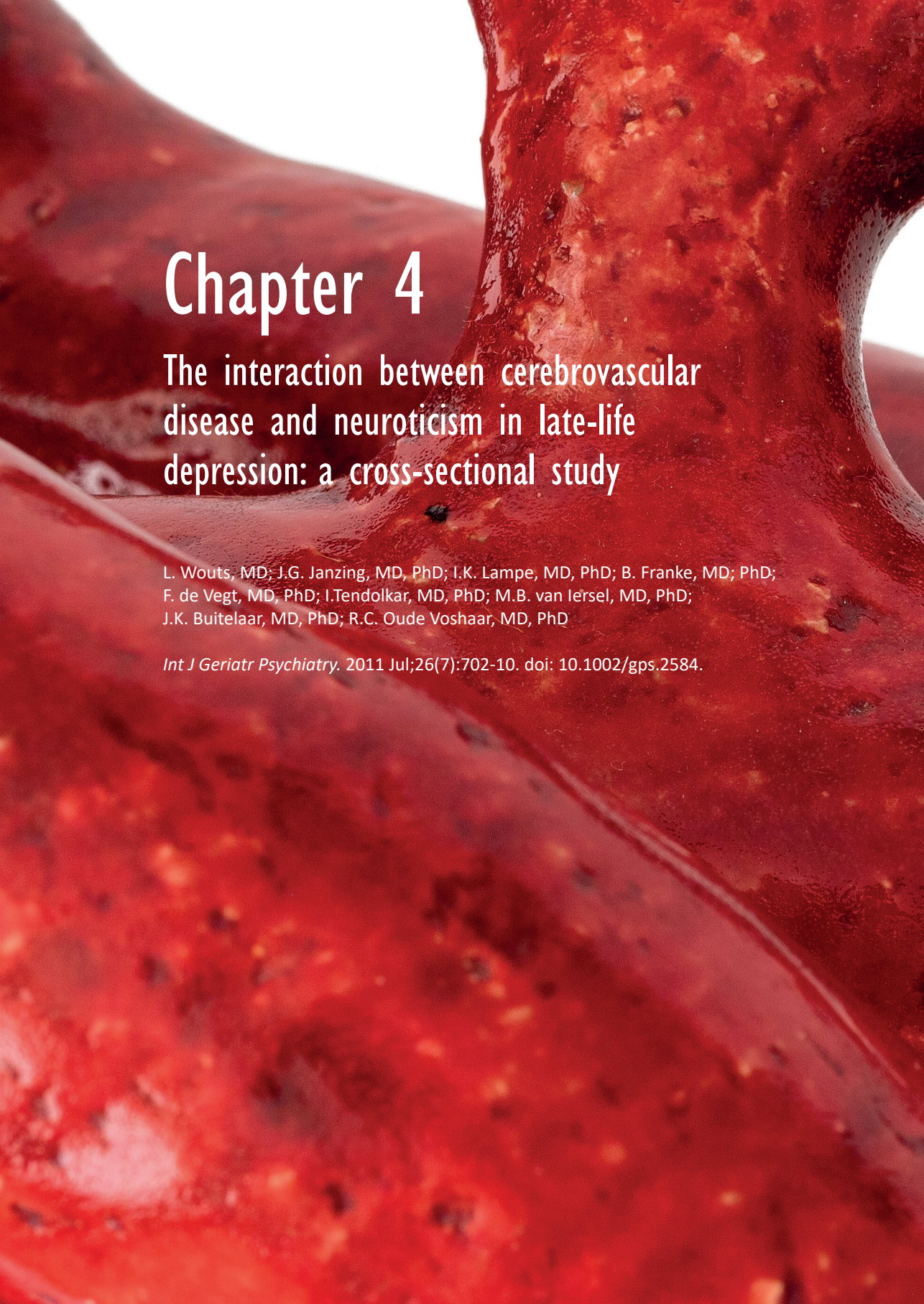
35. 35. Shipley BA, Weiss A, Der G, Taylor MD, Deary IJ. Neuroticism, extraversion, and mortality in the UK Health and Lifestyle Survey: a 21-year prospective cohort study. *Psychosom Med*. 2007;69(9):923-931. doi:10.1097/PSY.0B013E31815ABF83

36. Henderson KM, Clark CJ, Lewis TT, et al. Psychosocial distress and stroke risk in older adults. *Stroke*. 2013;44(2):367-372. doi:10.1161/STROKEAHA.112.679159

37. Prystowsky EN, Camm J, Lip GYH, et al. The impact of new and emerging clinical data on treatment strategies for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2010;21(8):946-958. doi:10.1111/J.1540-8167.2010.01770.X

38. Alexopoulos GS, Kiosses DN, Murphy C, Heo M. Executive dysfunction, heart disease burden, and remission of geriatric depression. *Neuropsychopharmacology*. 2004;29(12):2278-2284. doi:10.1038/SJ.NPP.1300557

39. Köhler S, Thomas AJ, Lloyd A, Barber R, Almeida OP, O'Brien JT. White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. *Br J Psychiatry*. 2010;196(2):143-149. doi:10.1192/BJP.BP.109.071399



# Chapter 4

## The interaction between cerebrovascular disease and neuroticism in late-life depression: a cross-sectional study

L. Wouts, MD; J.G. Janzing, MD, PhD; I.K. Lampe, MD, PhD; B. Franke, MD; PhD; F. de Vegt, MD, PhD; I.Tendolkar, MD, PhD; M.B. van Iersel, MD, PhD; J.K. Buitelaar, MD, PhD; R.C. Oude Voshaar, MD, PhD

*Int J Geriatr Psychiatry.* 2011 Jul;26(7):702-10. doi: 10.1002/gps.2584.

# Abstract

### Objective

Vascular disease and neuroticism are both risk-factors for late-life depression. In this study we examined the interaction between vascular disease and neuroticism as determinants of clinically relevant depressive symptoms (CRDS) in late-life.

### Methods

Multivariate logistic regression in a survey of 1396 population-dwelling people aged ≥70 years. CRDS were defined as scoring ≥16 on the CES-D. Vascular disease was categorised into 4 levels: none, ≥2 vascular risk factors, cardiac disease or stroke.

### Results

Neuroticism was strongly associated with CRDS in women (OR: 1.6, 95%-CI: 1.4-1.8). In men vascular disease, interacted negatively but significantly with neuroticism (cardiac disease by neuroticism: OR: 0.8, 95%-CI: 0.6-0.9; stroke by neuroticism: OR: 0.8, 95%-CI: 0.6-0.96) when predicting CRDS.

### Conclusions

In men vascular disease attenuates the predictive effect of neuroticism in CRDS, which might be mediated by apathy caused by cerebrovascular disease.

# Introduction

Late-life depression is a frequent and serious health problem, with reported prevalence rates of 1.8% for major and 10.2% for minor depression [1]. Depressed elderly patients are less healthy, they have more functional limitations, use health services more often and experience a lower quality of life than their non-depressed counterparts [2]. This makes knowledge about determinants of late-life depression highly relevant for patients, physicians and policy makers.

Since the prevalence of depression is higher in elderly with vascular disease, it has been hypothesized that cerebrovascular disease (CVD) plays a causative role in the incidence and persistence of depressive symptoms among older adults [3]. White matter hyperintensities (WMH) on MRI scans of the brain may reflect ischemia due to CVD [4]. The onset and outcome of depression have been associated with the volume of WMH [5 6]. Clinically, CVD can be evident or 'silent'. Associations between cerebrovascular risk factors (CVRF) and depression have been found [7 8 9 10 11]. CVRF can predict the volume of WMH [12 13 14] and as such can be used as a proxy for 'silent' CVD in epidemiological research.

The vascular depression hypothesis has stimulated research into biological predictors of depression, thereby often paying less attention to other theories of depression. Research of the role of personality in the onset of depression has shown that neuroticism is an important vulnerability factor for depression. Neuroticism is a stable trait that can be measured reliably, even in later life; it is not significantly affected by physical health [15]. Throughout life, a neurotic personality raises the odds with at least 49 % of developing depressive symptoms and major depression [16]. This effect of neuroticism is independent of age and has also been established in older people [17].

Since higher levels of neuroticism and CVRF/CVD often co-occur in patients with late-life depression, not only the impact of each of these vulnerability factors but also their interactions need to be studied. A positive interaction between CVRF/CVD and neuroticism would be likely since neuroticism raises the depressogenic effects of life-events [18] and physical illness [19]; and because neuroticism has a negative influence on adherence to medical treatment in cardiac and other patients [20 21]. So far the interaction between CVRF/CVD and neuroticism in models of late-life depression has only been studied in a small case-control design with negative results [22].

The objective of the present study was to investigate the interplay of vascular disease and neuroticism in explaining depression in later life in a large population sample. As both the prevalence of depression [23] and of its vulnerability factors-vascular disease and neuroticism- differ by gender [24 25] particular attention will be paid to sex-specific effects.

# Methods

## Sample

The present sample was drawn from the Nijmegen Biomedical Study (NBS), a population-based survey conducted in 2002 and 2003 by the Department of Epidemiology and Biostatistics and the Department of Clinical Chemistry of the Radboud University Nijmegen Medical Centre. 21756 Age- and sex- stratified randomly selected inhabitants of the municipality of Nijmegen received an invitation to fill out a postal questionnaire on, among others, lifestyle, and medical history, and to donate blood. The response to the initial questionnaire was 43 % in all age groups [26] and 40% in subjects aged 70 years and older. The response to additional questionnaires sent in 2004 and 2005 to all responders aged 70 years and older (N=2253) was 71% (N=1596). These additional questionnaires were used for the present study. Only information on the level of education and the smoking history were taken from the initial questionnaire. Exclusion criteria for the present study were a diagnosis of dementia or a history of bipolar disorder.

## Measurements

Depression - Clinically relevant depressive symptoms (CRDS) were measured by the 20-item Epidemiological Studies Depression scale (CES-D), and defined as a score of ≥16. The CES-D is a valid and widely used instrument for the detection of depressive symptoms [27]. The traditional cut-off of the CES-D (≥16), shows a sensitivity of 100% and a specificity of 88% for major depressive disorder in older inhabitants of the Netherlands [28].

Neuroticism - Neuroticism (range: 0-12) was measured using the Dutch version of the revised Eysenck Personality Questionnaire (EPQ-RSS) [29]. Results of the Dutch version of this questionnaire strongly resemble those of the English version [30]. The EPQ-RSS is based on a 3-factor model of personality: neuroticism, extraversion and psychoticism. Neuroticism is a stable personality trait that also in later life can be measured reliably as it is not significantly affected by physical health variables [15]. Nonetheless, an acute depression amplifies the personality profile of people prone to depression [31]. After recovery neuroticism decreases, but the overall shape of the profile doesn't change [32 33]. The relationship between change in personality and change in depressive symptoms is at most moderate and does not differ between men and women.

Cerebrovascular risk factors (CVRF) and cerebrovascular disease - Hypertension, diabetes mellitus, hypercholesterolemia, smoking, severe obesity, low physical activity and cardiac diseases were assessed, since they are well-documented as stroke risk factors [34 35]. Most of these CVRF were linked to depression in earlier studies [8 9 10 11]. Misclassification due to over reporting of hypertension, diabetes mellitus, hypercholesterolemia and cardiac diseases was reduced by requiring both a confirmative self-report and the use of appropriate medication for the specific disease. Participants were inquired about current smoking. Length and weight were asked for and body mass indexes were computed as follows: length/weight2 (m/kg2); severe obesity was defined as a BMI of ≥ 30 (m/kg2)[36].

Physical activity was measured using a short version of the Voorrips questionnaire counting household activities and sports. The use of tertiles to categorize a low, a medium or a high level of physical activity is validated for an elderly population living at home [37].

Acknowledging that in epidemiological research, self-reported CVRF and CVD are proxies for cerebrovascular lesions, we established a ranking in 4 levels on how closely they represent cerebrovascular damage:

- The reference group had none or 1 diagnosed cerebrovascular risk factor and no cardiac disease or cerebrovascular disease (level 0 in our ranking) .
- ' ≥2 vascular risk factors' consisted of ≥2 CVRF (hypertension, diabetes mellitus, hypercholesterolemia, smoking, severe obesitas, low physical activity) without evidence of cardiovascular or cerebrovascular disease. This category was ranked level 1. The use of this cut-off was based on statistical arguments: (1) this cut-off would result in large enough groups to study interactions; (2) a higher cut-off did not result in a larger association with depression (data not shown).
- 'Cardiac disease' was defined as myocardial infarction, angina pectoris, heart failure or atrial fibrillation) (level 2).
- Participants that had experienced a transient ischemic attack (TIA) or cerebrovascular accident (CVA) were classified as ' stroke' (level 3).
- When we use the term ' vascular disease' we refer to all 3 levels: ' ≥2 vascular risk factors'; 'cardiac disease' or 'stroke'.



## Possible confounders

In the knowledge that a history of depression, somatic comorbidity and sociodemographic variables predict a large portion of the variance of elderly major and subsyndromal depression in the general population [38] [39], the following possible confounders were assessed: age, educational level, marital status, disability, chronic diseases and a history of major depression. Educational level was based on the highest level of education completed by participants and coded low/medium/high. Marital status was asked for and dichotomized into 'currently living together with partner' or 'currently living alone'. Disability was established by asking if participants walked freely or used a stick or wheelchair outside. This variable was dichotomized into 'none' or 'some disability'. The self-reported presence of chronic lung disease, chronic kidney disease, chronic liver disease, Morbus Crohn or colitis ulcerosa, cancer and rheumatic arthritis or arthrosis were added to compute a composite score for somatic comorbidity. Three levels of somatic comorbidity were used: none; one comorbid disease; two or more comorbid diseases. This definition yielded (i) large enough groups and (ii) the highest univariate associations with depression. Furthermore, a self-reported history of treated lifetime depression (yes/no) was included as a covariate in the analysis.

## Statistical methods

Differences between the depressed and the non-depressed control group were tested with Pearson's Chi-square for categorical and dichotomous variables and Student's T-test

for continuous variables. The independent variables age and neuroticism were checked for linearity in the logit by a Box-Tidwell approach. In addition, all independent variables were checked for multicollinearity by Pearson's correlation coefficient. Missing data on covariates were treated by imputing the most reported value. Data were missing on: a history of depression (N=11; 0.8%), disability (N=12; 0.9%), education (N=10; 0.7%) or somatic comorbidity (N=28; 2.0%); the most reported value for all these variables was '0'. Differences in results for analyses with or without imputed data were checked as well as the effects of inclusion of dummy variables for missing data [40].

Models for depression were tested using multivariate logistic regression. First, we wanted to test if stratification by gender was needed. To do this, the influence of gender on the interaction between neuroticism and vascular disease was studied using a three way interaction factor (gender*neuroticism*vascular disease), while correcting for lower order interactions. Since gender significantly affected the interaction between vascular disease and neuroticism (see results) subsequent analyses were stratified by gender.

The robustness of the outcome was tested by leaving out outliers and influential cases in the solution and repeating the main analyses. In addition, the main analyses were repeated with different cut-off scores for the CES-D (15 and 17, respectively). Stepwise multivariate linear regression on the total CES-D score was performed using the same models. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 14.0.

## Results

Twenty four study participants were excluded; 15 because of a diagnosis of dementia and 9 because of a history of bipolar disorder. Furthermore, 176 participants were excluded due to missing data on CES-D score (N=133; 8%), on vascular disease (N=27; 2%) or on neuroticism (N=16, 1%), leaving a sample of 1396 elderly participants. Missing data on CESD-score, vascular disease or neuroticism were related to female sex, marital status (living alone), disability, a low or medium level of education, ≥2 chronic comorbid diseases and a higher age (all at a P value <.05). The men and women in the remaining study sample did not differ in age and consisted of 799 men and 597 women, of whom 103 men (13%) and 72 women (12%) were 85 years of age and older.

### Baseline characteristics and group differences

The study sample of 1396 elderly had a median age of 77.2 years (interquartile range) 73.3-81.5 years), 597 (42.8%) women participated in the study. In this population 291 (20.8%) had a CES-D score above cut-off. CRDS were significantly associated in univariate analyses with older age, female gender, marital status (living alone), a positive lifetime history of depression, lower education, presence of disability, higher levels of neuroticism, presence of cardiac disease and presence of stroke (Table 1). Correlations between all

independent variables were below Pearson's r=.40. No adaptations to our model were deemed necessary and the main analysis was performed as planned.

*Table 1. Baseline characteristics and group's differences between depressed and non-depressed participants*

| | | **Depressed (n=291)** | **Non-depressed (n=1105)** | **Depressed vs. Non-depressed** |
|---|---|---|---|---|
| *Variable* | | *Median (IQR)* | *Median (IQR)* | *Mean diff.(95%-CI)* |
| Age | *continuous* | 78.01 (73.4-83.2) | 77.0 (73.3-81.2) | 0.9 (0.2-1.6) |
| Neuroticism (0-12) | *continuous* | 5.5 (3.0-8.0) | 2.0 (1.0-4.0) | 3.1 (2.8-3.5) |
| *Variable* | | *Number (%)* | *Number (%)* | *OR (95%-CI)* |
| Sex | *male* | 134 (46.0) | 665 (60.2) | 1 |
| | *female* | 157 (54.0) | 440 (39.8) | 1.8 (1.4-2.3) |
| Marital Status | *currently living together* | 128 (44.0) | 707 (64.0) | 1 |
| | *currently living alone* | 163 (56.0) | 398 (36.0) | 2.3 (1.7-2.9) |
| History of Depression | *not present* | 253 (86.9) | 1038 (93.9) | 1 |
| | *present* | 38 (13.1) | 67 (6.1) | 2.3 (1.5-3.5) |
| Disability | *no* | 208 (71.5) | 885 (80.1) | 1 |
| | *present* | 83 (28.5) | 220 (19.9) | 1.6 (1.2-2.2) |
| Education | *low level (indicator)* | 185 (63.6) | 578 (52.3) | 1 |
| | *medium level* | 51 (17.5) | 228 (20.6) | 0.7 (0.5-1.0) |
| | *high level* | 55 (18.9) | 299 (27.1) | 0.6 (0.4-0.8) |
| Vascular disease | *none (indicator)* | 139 (47.8) | 588 (53.2) | 1 |
| | *≥2 vascular risk factors* | 31 (10.7) | 179 (16.2) | 0.7 (0.5-1.1) |
| | *cardiac disease* | 89 (30.5) | 254 (23.0) | 1.5 (1.1-2.0) |
| | *stroke* | 32 (11.0) | 84 (7.6) | 1.6 (1.03-2.5) |
| Other chronic diseases | *none (indicator)* | 139 (47.8) | 584 (52.9) | 1 |
| | *1 comorbid disease* | 112 (38.5) | 384 (34.8) | 1.2 (0.9-1.6) |
| | *≥2 comorbid diseases* | 40 (13.7) | 137 (12.4) | 1.2 (0.8-1.8) |

*Abbreviations*: IQR, interquartile range; 95%-CI, 95%-confidence interval; OR, odds ratio

## Three-way interaction between vascular disease, neuroticism and gender

The 291 subjects in the sample with CRDS (CESD-score ≥16) consisted of 135 men (45.8%) and 160 women (54.2%). As shown in Table 2, depressed men had lower mean neuroticism scores than depressed women. Women who suffered from CRDS reported lower levels of vascular disease than depressed men. Depressed women were living alone more often than depressed men; they more frequently reported a lower education, current disability and a comorbid disease (all at a P value <.05).

*Table 2. Differences between depressed men and women in the study sample*

| | | **Depressed Men (n=134)** | **Depressed Women (n=157)** | **Depressed Women vs. Men** |
|---|---|---|---|---|
| *Variable* | | *Median (IQR)* | *Median (IQR)* | *Mean diff.(95%-CI)* |
| Age | *continuous* | 78.2 (73.6-83.5) | 77.6 (73.2-82.6) | 0.0 (-1.4-1.4) |
| Neuroticism (0-12) | *continuous* | 4.7 (3.0-7.0) | 6.0 (4.0-8.0) | 1.4 (0.7-2.0) |
| *Variable* | | *Number (%)* | *Number (%)* | *OR (95%-CI)* |
| Marital Status | *currently living together* | 78 (58.2) | 50 (31.8) | 1 |
| | *currently living alone* | 56 (41.8) | 107 (68.2) | 3.0 (1.8-4.8) |
| History of Depression | *not present* | 122 (91.0) | 131 (83.4) | 1 |
| | *present* | 12 (9.0) | 26 (16.6) | 2.0 (0.98-4.2) |
| Disability | *no* | 109 (81.3) | 99 (63.1) | 1 |
| | *present* | 25 (18.7) | 58 (36.9) | 2.6 (1.5-4.4) |
| Education | *low level (indicator)* | 70 (52.2) | 115 (73.2) | 1 |
| | *medium level* | 26 (19.4) | 25 (15.9) | 0.6 (0.3-1.1) |
| | *high level* | 38 (28.4) | 17 (10.8) | 0.3 (0.1-0.5) |
| Vascular disease | *none (indicator)* | 55 (41.0) | 84 (53.5) | 1 |
| | *≥2 vascular risk factors* | 9 (6.7) | 22 (14.0) | 1.6 (0.7-3.7) |
| | *cardiac disease* | 51 (38.1) | 38 (24.2) | 0.5 (0.3-0.8) |
| | *stroke* | 19 (14.2) | 13 (8.3) | 0.4 (0.2-0.98) |
| Other chronic diseases | *none (indicator)* | 76 (56.7) | 50 (31.8) | 1 |
| | *1 comorbid disease* | 40 (29.9) | 85 (54.1) | 2.1 (1.3-3.6) |
| | *≥2comorbid diseases* | 18 (13.4) | 22 (14.0) | 0.8 (0.7-3.0) |

*Abbrevations*: IQR, interquartile range; diff, difference; 95%-CI, 95%-confidence interval

The first model included gender, age, education, marital status, a history of depression, disability and comorbid diseases as independent variables in a model for the prediction of CRDS. Adding neuroticism improved the model significantly (Chi-square: 267.8, p<0.001; Nagelkerke R2: 0.334). When vascular disease level 1, 2 and 3 was added the model was further improved (Chi-square: 11.8, p<0.01; Nagelkerke R2: 0.345). Next, a three-way interaction factor was added indicating gender-differences in the interaction between neuroticism and vascular disease, while correcting for possible lower-order interactions. This model was significantly better than the earlier model (Chi-square: 17.5, p<0.05; Nagelkerke R2: 0.366). These results supported stratification on gender to study the interaction between neuroticism and vascular disease.

## Interaction between vascular disease and neuroticism in women

In women neuroticism independently predicted CRDS (OR 1.6, 95%-CI: 1.4-1.8). A model for late-life CRDS in women that included age, marital status, history of depression, disability, education, comorbid diseases and neuroticism (Nagelkerke R2: 0.43) wasn't significantly improved by adding vascular disease levels or by adding factors for the interaction between neuroticism and vascular disease (Table 3).

*Table 3. Logistic regression of neuroticism, CVRF and their interaction factor on depression, separately for men en women*

| | **Men (n=799)** | | **Women (n=597)** | |
|---|---|---|---|---|
| *Variable* | *OR* | *95%-CI* | *OR* | *95%-CI* |
| ≥2 Vascular risk factors | 0.7 | 0.1-3.4 | 0.5 | 0.1-2.0 |
| Cardiac disease | 4.2 | 1.8-10.0 | 1.1 | 0.3-3.7 |
| Stroke | 5.0 | 1.5-16.2 | 0.01 | 0.0-2.6 |
| Neuroticism (range 0-12) | 1.7 | 1.5-1.9 | 1.6 | 1.4-1.8 |
| Neuroticism by ≥*2 vascular risk factors* | 0.9 | 0.7-1.2 | 1.0 | 0.8-1.3 |
| Neuroticism by *cardiac disease* | 0.8 | 0.6-0.9 | 1.0 | 0.8-1.3 |
| Neuroticism by *stroke* | 0.8 | 0.6-0.96 | 2.3 | 0.9-6.1 |
| Age | 1.0 | 0.9-1.0 | 1.0 | 1.0-1.1 |
| Educational level (medium) | 0.9 | 0.5-1.6 | 0.7 | 0.4-1.4 |
| Educational level (high) | 1.1 | 0.7-1.8 | 0.4 | 0.2-0.9 |
| Marital status | 2.4 | 1.5-3.7 | 1.9 | 1.1-3.1 |
| Disability | 0.9 | 0.5-1.6 | 1.1 | 0.6-1.9 |
| Chronic diseases (one) | 0.8 | 0.5-1.3 | 1.1 | 0.7-1.9 |
| Chronic diseases (two or more) | 0.8 | 0.4-1.6 | 0.7 | 0.4-1.5 |
| History of major depression | 1.2 | 0.6-2.6 | 2.0 | 0.9-4.2 |

*Abbreviations*: CVRF, cerebrovascular risk factors
Note Adjusted for age, marital status, educational level, comorbidity, disability and history of depression

Men: Chi-square for Model with vs. Model without interaction factor: 9.31; p=0.03

Nagelkerke R square 0.28; Cox & Snell R square 0.17.

Women: Chi-square for Model with vs. Model without interaction factor: 5.70; p=0.13

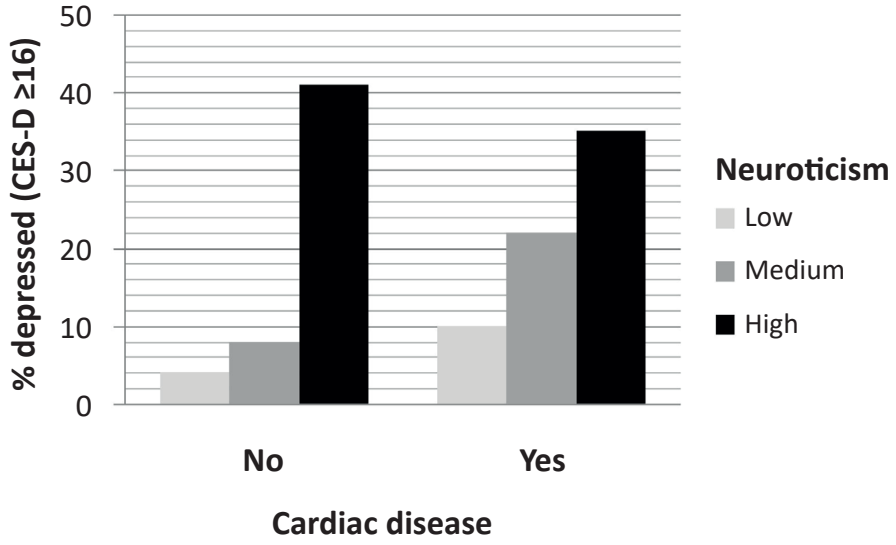
Nagelkerke R square 0.44; Cox & Snell R square 0.31.

### Interaction between vascular disease and neuroticism in men

In men the best fitting model included interaction factors of neuroticism by vascular disease level (Chi-square 9.3, p<0.05; Nagelkerke R2: 0.28). As shown in figure 1 and table 3, in men when vascular disease was present, neuroticism was less predictive of CRDS (neuroticism by cardiac disease: OR: 0.8, 95%-CI: 0.6-0.9; neuroticism by stroke: OR: 0.8, 95%-CI: 0.6-0.96).

Leaving out outliers or influential cases, changing the cut-off of the CES-D to 17 or performing a multivariate linear regression on depressive symptoms all gave similar results.

*Figure 1. Negative interaction between cardiac disease and neuroticism in the prediction of depression in men*




## Discussion

The results of this study show that gender influences the interaction between vascular disease and neuroticism in late-life CRDS. In men the presence of vascular disease seemed to reduce the association between neuroticism and CRDS. In women a main effect of neuroticism was present, but neither a main effect of vascular disease, nor an interaction effect between vascular disease and neuroticism was seen.

### Gender differences

As expected, the level of neuroticism was higher in women compared to men and the prevalence of vascular disease was higher in men compared to women. The significant

three-way interaction between gender, neuroticism and vascular disease, supported our stratification for gender in subsequent analyses on the combined effects of vascular disease and neuroticism. In women, no relationship could be detected between vascular disease and CRDS, in contrast to men. This gender-difference in the effect of vascular disease might be explained by the fact that in women the same stage of vascular disease is present at a later age (10-15 years) than in men [41]. Furthermore, vascular diseases in women have a different presentation and are not as well detected as in men [25]. However, these explanations should be interpreted cautiously because there was a small number of depressed women with both vascular disease and a low level of neuroticism in this study.

In elderly men we found a negative interaction between vascular disease and neuroticism. A high level of vascular disease did reduce rather than raise the depressogenic potential of neuroticism in this large epidemiological study. This adds credibility to similar results from a small case-control design in a mixed gender population [22]. This negative interaction effect between neuroticism and vascular disease clearly differs from the positive interaction effects between neuroticism and life events [18] or disability [19] which led to raise the levels of depressive symptoms.



How could we explain the negative interaction effect between neuroticism and cardiac disease in men? There is the possibility of a ceiling effect at the highest levels of both neuroticism and cardiac disease, suggesting that some pathways in which vascular disease leads to depressive symptoms are shared with pathways of neuroticism. Common pathways could be inflammatory processes [42 43 44] and (associated) hypothalamic-pituitary-adrenal axis functioning [45 46 47].

Our results suggest that, in men, the biological changes that occur in the brain because of vascular disease override some of the independent pathways of neuroticism to depressive symptoms. A similar mechanism was seen by Archer et al. (2007) [48]: in their study the presence of Alzheimer's disease attenuated the association between neuroticism and depression. Several studies have shown that vascular disease is associated with apathy [49 50]. We speculate that the presence of apathy might temper the effect of neuroticism by reducing attention or reducing responsiveness to stress. This would be an interesting topic for future research.

## Limitations

There are some limitations to these results. First, the direction of relationships could not be established because of the cross-sectional design of this study. Secondly, self-report measurements were used. And although the CES-D is a well-validated measurement for the detection of depressive symptoms in the elderly, its specificity for major depression is less than 100% (namely 88%, following Beekman et al. 1997) [28]. However, subsyndromal depressive states form a continuum with major depression, also with regard to the relationship with neuroticism [51 18]. Self-reported vascular disease has been compared with physician reports in a number of studies. Very good concordance has been found for self-reported and physician reported diabetes mellitus, good concordance for hypertension

and cardiovascular disease and moderate concordance for cerebrovascular disease [52 53 54]. However, we only accounted for already diagnosed diseases, probably missing underdiagnosed diseases (for example underdiagnosed diabetes) [55]. There are also benefits of using self-report measurements in a cross-sectional design: relationships can be studied in a large non-clinical population at relatively low costs. A third limitation might be a bias due to selective dropout of the physically frail elderly women. However, because of stratification for age at enrolment in the NBS, this study still included a large sample of the very old, which is often missed in other studies.

Strengths of this study include the use of different levels of vascular disease according to association with cerebrovascular damage, which gave more insight than a composite score would have done. In addition, we corrected for disability and comorbid (non-vascular) chronic diseases, which mediated the relationship between vascular disease and depression in some previous reports [56]. Though our data clearly support the important role of vascular disease, they also highlight the necessity to broaden the risk model of late-life depression. Gender-differences in the associations between vascular disease and depression and gender-differences in the role of an interaction between vascular disease and neuroticism could explain some negative or inconsistent findings in mixed-populations [57 58 59].

## Final conclusion

We conclude that in elderly women with CRDS the predictive value of (self-reported) vascular disease is not as large as in men of similar age. In men with both vascular disease and a high level of neuroticism, the effect of neuroticism was tempered, maybe by the presence of apathy. A future aim should be to replicate and extend the results of this study in a longitudinal design.

## Acknowledgements

Principal investigators of the Nijmegen Biomedical Study are L.A.L.M. Kiemeney, M. den Heijer, A.L.M. Verbeek, D.W. Swinkels en B. Franke.

## References


1. Beekman ATF, Copeland JRM, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry*. 1999;174(APR.):307-311. doi:10.1192/BJP.174.4.307
2. Herrman H, Patrick DL, Diehr P, et al. Longitudinal investigation of depression outcomes in primary care in six countries: the LIDO Study. Functional status, health service use and treatment of people with depressive symptoms. *Psychol Med*. 2002;32(5):889-902. doi:10.1017/S003329170200586X
3. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. "Vascular depression" hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915-922. doi:10.1001/archpsyc.1997.01830220033006
4. Fernando MS, Simpson JE, Matthews F, et al. White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. *Stroke*. 2006;37(6):1391-1398. doi:10.1161/01.STR.0000221308.94473.14
5. De Groot JC, De Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MMB. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry*. 2000;57(11):1071-1076. doi:10.1001/ARCHPSYC.57.11.1071
6. Taylor WD, Steffens DC, MacFall JR, et al. White matter hyperintensity progression and late-life depression outcomes. *Arch Gen Psychiatry*. 2003;60(11):1090-1096. doi:10.1001/ARCHPSYC.60.11.1090
7. Bruce DG, Casey G, Davis WA, et al. Vascular depression in older people with diabetes. *Diabetologia*. 2006;49(12):2828-2836. doi:10.1007/S00125-006-0478-Y
8. Holley C, Murrell SA, Mast BT. Psychosocial and vascular risk factors for depression in the elderly. *Am J Geriatr Psychiatry*. 2006;14(1):84-90. doi:10.1097/01.JGP.0000192504.48810.CB
9. Krishnan KRR, Taylor WD, McQuoid DR, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biol Psychiatry*. 2004;55(4):390-397. doi:10.1016/J.BIOPSYCH.2003.08.014
10. Mast BT, Neufeld S, MacNeill SE, Lichtenberg PA. Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *Am J Geriatr Psychiatry*. 2004;12(1):93-101. Accessed July 13, 2022. https://pubmed-ncbi-nlm-nih-gov.proxy-ub.rug.nl/14729564/
11. Mast BT, Azar AR, Murrell SA. The vascular depression hypothesis: the influence of age on the relationship between cerebrovascular risk factors and depressive symptoms in community dwelling elders. *Aging Ment Health*. 2005;9(2):146-152. doi:10.1080/13607860412331336832
12. Jeerakathil T, Wolf PA, Beiser A, et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke*. 2004;35(8):1857-1861. doi:10.1161/01.STR.0000135226.53499.85

13. Lee SC, Park SJ, Ki HK, et al. Prevalence and risk factors of silent cerebral infarction in apparently normal adults. *Hypertens (Dallas, Tex 1979)*. 2000;36(1):73-77. doi:10.1161/01.HYP.36.1.73-A

14. Lindgren A, Roijer A, Rudling O, et al. Cerebral lesions on magnetic resonance imaging, heart disease, and vascular risk factors in subjects without stroke. A population-based study. *Stroke*. 1994;25(5):929-934. doi:10.1161/01.STR.25.5.929

15. Steunenberg B, Twisk JWR, Beekman ATF, Deeg DJH, Kerkhof AJFM. Stability and change of neuroticism in aging. *J Gerontol B Psychol Sci Soc Sci*. 2005;60(1). doi:10.1093/GERONB/60.1.P27

16. Kendler KS, Gatz M, Gardner CO, Pedersen NL. Personality and major depression: a Swedish longitudinal, population-based twin study. *Arch Gen Psychiatry*. 2006;63(10):1113-1120. doi:10.1001/ARCHPSYC.63.10.1113

17. Steunenberg B, Beekman ATF, Deeg DJH, Kerkhof AJFM. Personality and the onset of depression in late life. *J Affect Disord*. 2006;92(2-3):243-251. doi:10.1016/J.JAD.2006.02.003

18. Ormel J, Oldehinkel AJ, Brilman EI. The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *Am J Psychiatry*. 2001;158(6):885-891. doi:10.1176/APPI.AJP.158.6.885

19. Lyness JM, Heo M, Datto CJ, et al. Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. *Ann Intern Med*. 2006;144(7):496-504. doi:10.7326/0003-4819-144-7-200604040-00008

20. Evangelista LS, Berg J, Dracup K. Relationship between psychosocial variables and compliance in patients with heart failure. *Heart Lung*. 2001;30(4):294-301. doi:10.1067/MHL.2001.116011

21. Glazer KM, Emery CF, Frid DJ, Banyasz RE. Psychological predictors of adherence and outcomes among patients in cardiac rehabilitation. *J Cardiopulm Rehabil*. 2002;22(1):40-46. doi:10.1097/00008483-200201000-00006

22. Oldehinkel AJ, Ormel J, Brilman EI, Van Den Berg MD. Psychosocial and vascular risk factors of depression in later life. *J Affect Disord*. 2003;74(3):237-246. doi:10.1016/S0165-0327(02)00014-9

23. Kendler KS, Gardner CO, Neale MC, Prescott CA. Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? *Psychol Med*. 2001;31(4):605-616. doi:10.1017/S0033291701003907

24. Goodwin RD, Gotlib IH. Gender differences in depression: the role of personality factors. *Psychiatry Res*. 2004;126(2):135-142. doi:10.1016/J.PSYCHRES.2003.12.024

25. Pilote L, Dasgupta K, Guru V, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ*. 2007;176(6). doi:10.1503/CMAJ.051455

26. Hoogendoorn EH, Hermus AR, De Vegt F, et al. Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. *Clin Chem*. 2006;52(1):104-111. doi:10.1373/CLINCHEM.2005.055194

27. Radloff LS, Teri L. Use of the Center of Epidemiological Studies-depression scale with older adults. *Clin Gerontol*. 1986;(5):119-136.

28. Beekman ATF, Deeg DJH, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med*. 1997;27(1):231-235. doi:10.1017/S0033291796003510

29. Eysenck SBG, Eysenck HJ, Barrett P. A revised version of the psychoticism scale. *Pers Individ Dif*. 1985;6(1):21-29. doi:10.1016/0191-8869(85)90026-1

30. Sanderman R, Eysenck, S.B.G., Arrindell WA. Cross-cultural comparisons of personality: the Netherlands and England. *Psychol Rep*. 1991;69(8):1091. doi:10.2466/pr0.69.8.1091-1096

31. Ormel J, Oldehinkel AJ, Vollebergh W. Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Arch Gen Psychiatry*. 2004;61(10):990-996. doi:10.1001/ARCHPSYC.61.10.990

32. Costa PT, Bagby RM, Herbst JH, McCrae RR. Personality self-reports are concurrently reliable and valid during acute depressive episodes. *J Affect Disord*. 2005;89(1-3):45-55. doi:10.1016/J.JAD.2005.06.010

33. Santor DA, Bagby RM, Joffe RT. Evaluating stability and change in personality and depression. *J Pers Soc Psychol*. 1997;73(6):1354-1362. doi:10.1037//0022-3514.73.6.1354

34. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37(6):1583-1633. doi:10.1161/01.STR.0000223048.70103.F1

35. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22(3):312-318. doi:10.1161/01.STR.22.3.312

36. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. *Gastroenterology*. 2007;132(6):2087-2102. doi:10.1053/J.GASTRO.2007.03.052

37. Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. *Med sci Sport Exerc*. 1991;23(8):974-979.

38. Harris T, Cook DG, Victor C, DeWilde S, Beighton C. Onset and persistence of depression in older people--results from a 2-year community follow-up study. *Age Ageing*. 2006;35(1):25-32. doi:10.1093/AGEING/AFI216

39. Schoevers RA, Beekman ATF, Deeg DJH, Geerlings MI, Jonker C, Van Tilburg W. Risk factors for depression in later life; results of a prospective community based study (AMSTEL). *J Affect Disord*. 2000;59(2):127-137. doi:10.1016/S0165-0327(99)00124-X

40. Tabachnick BG, Fidell LS. *Using Multivariate Statistics Title: Using Multivariate Statistics*. 5th ed. Pearson Education; 2005. https://lccn.loc.gov/2017040173

41. Bittner V. Perspectives on dyslipidemia and coronary heart disease in women. *J Am Coll Cardiol*. 2005;46(9):1628-1635. doi:10.1016/J.JACC.2005.05.089

42. Bouhuys AL, Flentge F, Oldehinkel AJ, Van Den Berg MD. Potential psychosocial mechanisms linking depression to immune function in elderly subjects. *Psychiatry Res*. 2004;127(3):237-245. doi:10.1016/J.PSYCHRES.2004.05.001

43. Dimopoulos N, Piperi C, Salonicioti A, et al. Elevation of plasma concentration of adhesion molecules in late-life depression. *Int J Geriatr Psychiatry*. 2006;21(10):965-971. doi:10.1002/GPS.1592

44. Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O'Brien JT. Increase in interleukin-1beta in late-life depression. *Am J Psychiatry*. 2005;162(1):175-177. doi:10.1176/APPI.AJP.162.1.175

45. McCleery JM, Goodwin GM. High and low neuroticism predict different cortisol responses to the combined dexamethasone--CRH test. *Biol Psychiatry*. 2001;49(5):410-415. doi:10.1016/S0006-3223(00)01056-8

46. Pace TWW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain Behav Immun*. 2007;21(1):9-19. doi:10.1016/J.BBI.2006.08.009

47. Zobel A, Barkow K, Schulze-Rauschenbach S, et al. High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic-pituitary-adrenocortical system in healthy volunteers. *Acta Psychiatr Scand*. 2004;109(5):392-399. doi:10.1111/J.1600-0447.2004.00313.X

48. Archer N, Brown RG, Reeves SJ, et al. Premorbid personality and behavioral and psychological symptoms in probable Alzheimer disease. *Am J Geriatr Psychiatry*. 2007;15(3):202-213. doi:10.1097/01.JGP.0000232510.77213.10

49. Lavretsky H, Zheng L, Weiner MW, et al. The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. *Int J Geriatr Psychiatry*. 2008;23(10):1040-1050. doi:10.1002/gps.2030

50. van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry*. 2008;23(3):266-271. doi:10.1002/GPS.1872

51. Hermens MLM, Van Hout HPJ, Terluin B, et al. The prognosis of minor depression in the general population: a systematic review. *Gen Hosp Psychiatry*. 2004;26(6):453-462. doi:10.1016/J.GENHOSPPSYCH.2004.08.006

52. Kehoe R, Wu SY, Leske MC, Chylack LT. Comparing self-reported and physician-reported medical history. *Am J Epidemiol*. 1994;139(8):813-818. doi:10.1093/OXFORDJOURNALS.AJE.A117078

53. Kriegsman DMW, Penninx BWJH, Van Eijk JTM, Boeke AJP, Deeg DJH. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol*. 1996;49(12):1407-1417. doi:10.1016/S0895-4356(96)00274-0

54. Tretli S, Lund-Larsen PG, Foss OP. Reliability of questionnaire information on cardiovascular disease and diabetes: cardiovascular disease study in Finnmark county. *J Epidemiol Community Health*. 1982;36(4):269-273. doi:10.1136/JECH.36.4.269

55. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care*. 2009;32(2):287-294. doi:10.2337/DC08-1296

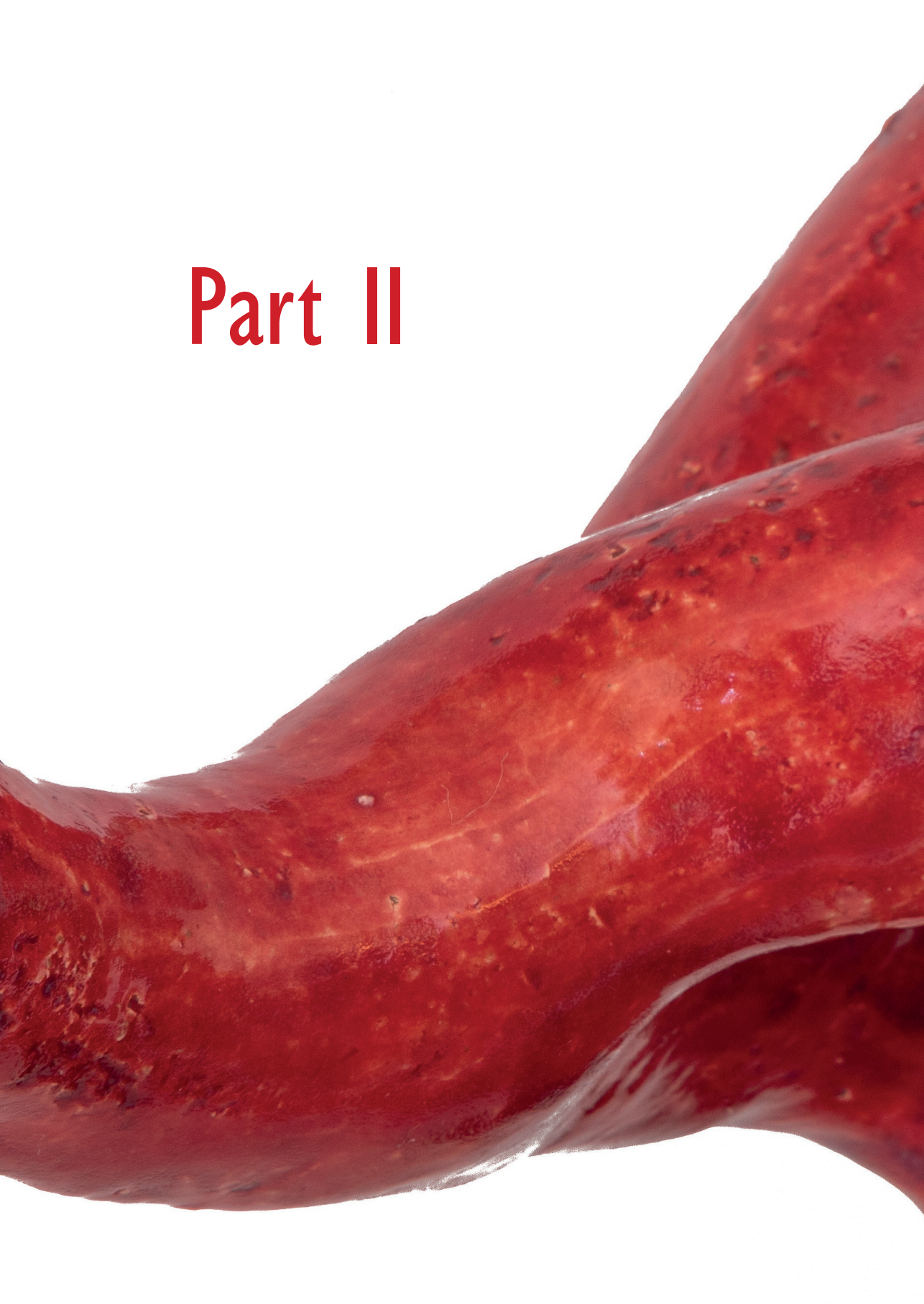
56. Sanders MLS, Lyness JM, Eberly S, King DA, Caine ED. Cerebrovascular risk factors, executive dysfunction, and depression in older primary care patients. *Am J Geriatr Psychiatry*. 2006;14(2):145-152. doi:10.1097/01.JGP.0000192482.27931.1E

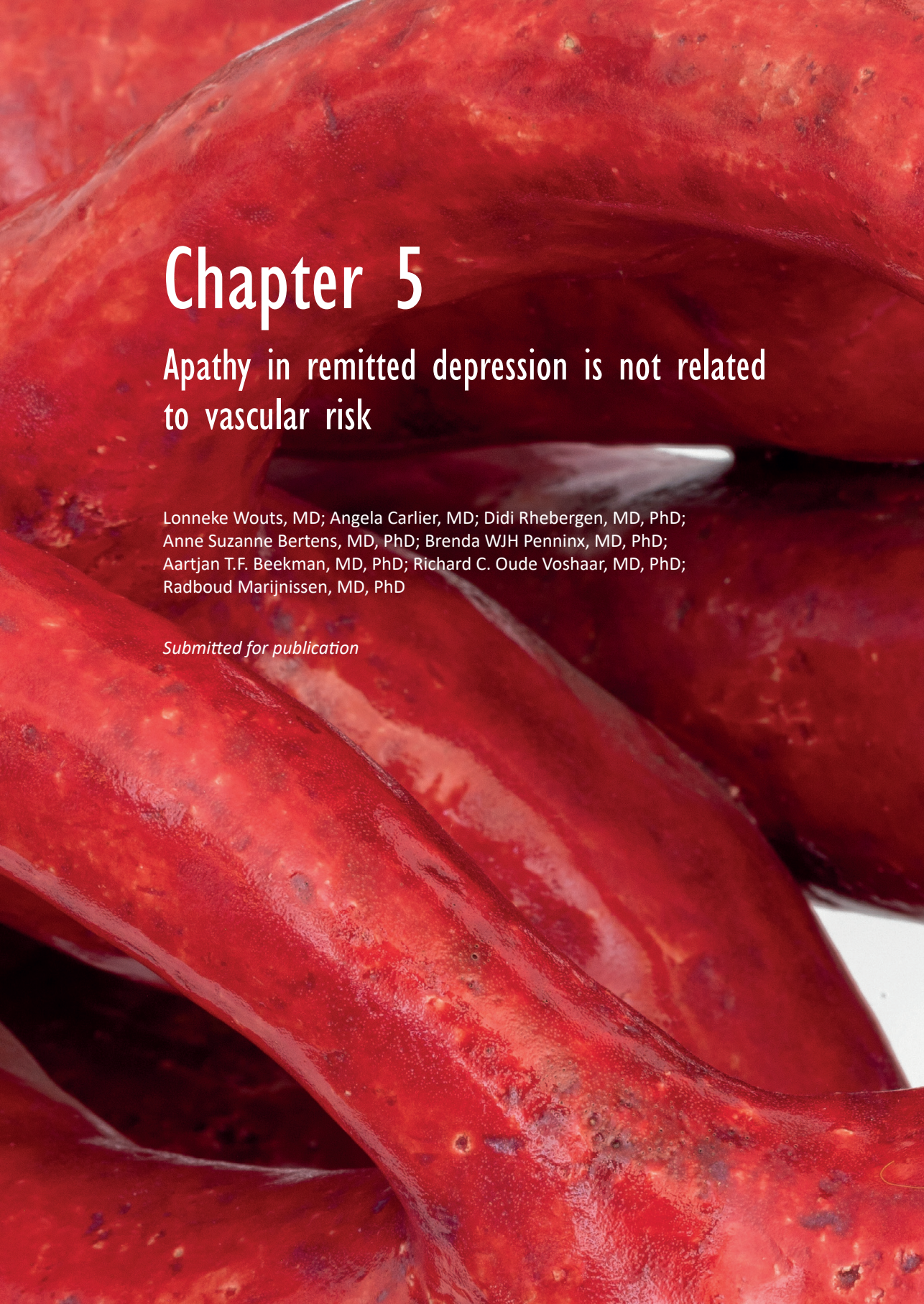
57. Cervilla J, Prince M, Rabe-Hesketh S. Vascular disease risk factors as determinants of incident depressive symptoms: a prospective community-based study. *Psychol Med*. 2004;34(4):635-641. doi:10.1017/S0033291703001533

58. Lyness JM, Caine ED, King DA, Conwell Y, Cox C, Duberstein PR. Cerebrovascular risk factors and depression in older primary care patients: testing a vascular brain disease model of depression. *Am J Geriatr Psychiatry*. 1999;7(3):252-258. doi:10.1097/00019442-199908000-00010

59. Nuyen J, Spreeuwenberg PM, Beekman ATF, Groenewegen PP, van den Bos GAM, Schellevis FG. Cerebrovascular risk factors and subsequent depression in older general practice patients. *J Affect Disord*. 2007;99(1-3):73-81. doi:10.1016/J.JAD.2006.08.011

# Part II





# Chapter 5

## Apathy in remitted depression is not related to vascular risk

Lonneke Wouts, MD; Angela Carlier, MD; Didi Rhebergen, MD, PhD; Anne Suzanne Bertens, MD, PhD; Brenda WJH Penninx, MD, PhD; Aartjan T.F. Beekman, MD, PhD; Richard C. Oude Voshaar, MD, PhD; Radboud Marijnissen, MD, PhD

*Submitted for publication*

# Abstract

## Background

Despite successful treatment of depressive disorder many patients continue to suffer from residual symptoms. Since (cerebro)vascular disease is a determinant of depression as well as apathy, we hypothesized that apathy in remitted depression is related to comorbid vascular disease.

## Methods

Among a well-defined, prospective cohort of 1523 depressed patients, we cross-sectionally studied, whether vascular risk factors and diseases were associated with apathy among those 663 participants who achieved a full-remission at 6-year follow-up. Depressive disorders were assessed according to DSM-IV criteria applying the Composite International Diagnostic Interview (CIDI) at baseline and follow-up. Multiple linear regression analyses were applied to study the association between vascular risk factors and diseases (independent variables) and apathy (dependent variable), adjusted for confounders including residual depressive symptoms. Apathy was measured with the Starkstein Apathy Scale (SAS) as well as apathy dimensions identified by principal component analysis (PCA) on the item-scores of the SAS and Inventory of Depressive Symptomatology (IDS).

## Results

Among the 663 participants (mean age (SD): 46.5 (16.1) years; 66.5% females) none of the vascular risk factors (blood pressure, ankle brachial index, body mass index, smoking and diabetes mellitus) or vascular diseases (cardiac disease, cerebrovascular accidents) were associated with apathy, neither the SAS sum score, nor both apathy factors we identified by the PCA.

## Limitations

Neuroimaging would have provided more information.

## Conclusions

Apathy in remitted depression is not associated with vascular damage. (233)

# Introduction

Despite successful treatment of a depressive episode, many patients still suffer from residual symptoms placing them at an increased risk of relapse [1 2]. A frequently observed residual symptom by depressed patients who achieved remission is apathy [3 4].
Apathy is generally considered a lack of goal-directed behavior, cognition and/or emotion [5]. Over the past decades, apathy has been identified as a common and clinically relevant behavioral syndrome in many neuropsychiatric disorders [6]. While symptoms and signs of apathy are highly common among depressed patients [7], studies on apathy in depression are scarce.
In the Netherlands Study of Depression in Older Persons (NESDO) 199/266 (75%) of depressed patients had a clinically relevant level of apathy at baseline. Of these apathic depressed patients, at two-year follow-up, 80% were still classified as apathic, while only 41% was still depressed. Moreover, among the non-apathic depressed patients at baseline, 36% became apathic at follow-up [7]. These figures are alarming, as apathy predicts a lower return to work after remitted depression [8]. These findings corroborate findings that a low interest in work and activities are among the most frequently encountered residual symptoms in remitted depression [9 10].

Empirical studies on apathy in depression, however, are easily confounded due to overlap in symptoms and signs. Considering the symptom-domain level of apathy, apathy is described as a loss of initiative in behavioral terms, and as loss of interest or anhedonia in cognitive/emotional terms [11 12]. The observed 'inability to want' has also been defined as amotivation [11]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; 2013) loss of interest and anhedonia is a core criterion of a depressive disorder next to or in addition to depressed mood. Furthermore, the observable reduction in physical activity among depressed patients may easily be confused with or be a result of a loss of initiative. To avoid bias due to overlapping criteria, studies on apathy in remitted depression should adjust for the residual level (severity) of pure 'mood' symptoms, without correcting for loss of interest, anhedonia and a reduction of physical activity (see methods).

From a neurobiological perspective, apathy is related to dysfunctioning of prefrontal-basal ganglia circuitries [13]. Neuroimaging studies have shown that the frontal regions with their projections to prefrontal regions, and the basal ganglia, the parietal regions, and the anterior cingulate play a role in planning, motivation, and auto-activation [14]. Structural damage of these regions and projections, as seen in Alzheimer's disease [15] or functional impairment of these, as seen in Parkinson's disease (dopaminergic and serotonergic depletion) [16] are associated with apathy. Apathy in late-life depression has also been related to structural damage [17 18]; although the depressive symptoms that overlap with apathy (anhedonia, loss of interest and an observable reduction in physical activity) in theory would be linked with functional impairment of the frontolimbic networks. Apathy during a depression and persisting after seemingly successful depression treatment has been linked to structural damage to the frontolimbic network [19] ; and with persisting abnormalities in the salience network [20].

The vascular apathy hypothesis poses that the generally widespread cerebrovascular damage due to small vessel disease causes damage to the frontolimbic networks, even if no other symptoms of cerebrovascular disease are yet present and the cerebrovascular damage is still subclinical [21 22 23]. While empirical evidence for this hypothesis is still scarce, it might explain the structural damage found in apathy persisting after depression [19 20].

The objective of the present study is to assess the association between comorbid vascular risk factors and vascular diseases and the severity of apathy at 6-year follow-up among a large cohort of well-phenotyped depressed patients who had achieved a full remission according to DSM criteria. Within this unique study design, we hypothesize that apathy in remitted depression is associated with vascular risk factors and vascular disease, and we hypothesize that this association is not explained by the residual symptom of a depressed mood.

# Methods

## Design and participants

The present study was embedded in the Netherlands Study of Depression and Anxiety (NESDA) [24 25] and the Netherlands Study of Depression in Older Persons (NESDO) [26].
NESDA and NESDO are multi-site naturalistic prospective clinical cohort studies that have harmonized their study design and measurements. Depressive disorder was assessed over a 6-month according to DSM-IV criteria based on the Clinical International Diagnostic Interview, version 2.1 (CIDI 2.1) at both baseline and 6-year follow-up [27 28]. From the 1523 patients with a past 6-month depressive disorder at baseline we selected all patients that had no past 6-month depressive disorder according to DSM-IV criteria at 6-year follow-up (n=663). We have chosen the 6-year follow-up assessment for our analyses as both cohort studies had included the Starkstein Apathy Scale at this assessment.

For details of patient recruitment, attrition rates and study design we refer to previous papers of both cohort studies [25 24 26]. Of particular relevance for the present study, however, is that dementia was specifically an exclusion criterion of the NESDO study, defined as an established diagnosis of dementia, a Mini Mental State Examination (MMSE) <18 (allowing to include also severely depressed patients), and a suspected diagnosis of dementia underlying the depression by the referring geriatric psychiatrist. Since these latter criteria were not applied in the NESDA study due to an upper age-limit of 65 years, we additionally checked the general practitioner's information of the NESDA participants for a diagnosis of either Alzheimer's disease or multi-site infarct dementia (these were not found).

## Measures

### Primary outcome measure- apathy

The presence and severity of apathy at the 6-year follow-up was assessed by means of the self-report version of the 14-item Starkstein apathy scale (SAS) [29]. This scale is well-validated and a score of ≥14 is considered to indicate severe apathy [30].

Depressive symptom severity was assessed with the Inventory of Depressive Symptomatology-Self Report (IDS-SR), a well-validated depressive symptom questionnaire [31 32].

Since the sum score of the SAS and IDS strongly correlated (r=0.47, p<.001), we decided to conduct sensitivity analyses based on the apathy and mood dimensions revealed by a principal component analysis (PCA) on all items of the SAS and the IDS using their original four-point Likert scale. We applied an oblimin rotation with Kaiser normalization and replaced missing item-data by means. Identified apathy and mood factors were computed by using the Anderson-Rubin method and used as dependent variables in the regression analyses.
We checked for robustness by performing principal component analyses on the SAS and IDS with dichotomized answers, as well as by performing the PCA for both scales separately. These additional sensitivity analyses did not change the factor solution presented in the Supplemental Information.

As shown in the supplemental material, we identified two apathy factors, i.e., amotivation and loss of initiative, and one mood factor.
Items that loaded (>0.4) on the amotivation factor were “Are you interested in new things?”, “Does anything interest you?”, “Do you put much effort into things?”, “Are you always looking for something to do?”, “Do you have plans and goals for the future?”, and: “Do you have motivation?”.
Items that loaded (>0.4) on the initiative factor were “Does someone has to tell you what to do each day?”, “Are you indifferent to things?”, “Are you unconcerned with many things?”, “Do you need a push to get started on things?”, “Are you neither happy nor sad, just in between?”, and:” Would you consider yourself apathetic?”.
Items that loaded (>0.4) on the mood factor were “Feeling sad”, “Feeling irritable”, “Feeling anxious or tense”, “Response of your mood to good or desired events”, “The quality of your mood”, “Concentration/decision Making”, “View of myself”, “View of my future”, “Thoughts of death or suicide”, “General interest”.
Both apathy factors were used as primary outcome variables in the analyses, whereas the mood factor was included as a covariate to adjust for confounding.

## Determinants

Vascular risk factors - During a standardized medical examination at the 6-year follow-up [33] [25], we assessed smoking status and measured systolic and diastolic blood pressure (mmHg) twice in a supine position using an electronic Omron sphygmomanometer. Length (cm) and weight (kg) were measured to calculate the body-mass index (BMI) as a measure of obesity. Doppler assessment of ankle and blood pressure allowed calculation of the ankle-brachial index (ABI)[34] as a measure of atherosclerosis [35].
Vascular diseases - The presence of diabetes mellitus, and past/current history of stroke and cardiac disease were derived from the answers to the self-report questions of the CBS/LASA-questionnaire (NESDO) [36] and on information provided by the primary-care physician (NESDA) at the 6-year follow-up.

## Covariates

The following covariates were controlled for as these might confound the association between vascular risk factors and diseases and apathy.
Age, sex, and highest level of education were documented at the baseline interview. The highest level of education was categorized as basic, intermediate and high.
The use of antipsychotics, antidepressants and benzodiazepines was asked during the interview and checked for by inspection of medication containers. Handgrip strength (kg) was assessed with a dynamometer as indicator of physical performance [37].
Finally, the mood factor (see above) was included as a covariate to adjust for residual (and overlap of apathy with) depression.

## Statistical analyses

Multiple linear regression models were built for the SAS sum score as well as for both apathy factors (dependent variables) separately. All vascular risk factors and vascular diseases were examined as cerebrovascular-related independent variables in separate models, adjusted for covariates described above including the level of residual depressive symptoms (based on either the IDS or the mood factor identified by the PCA). Missing values on any of the covariates were replaced by their means. To adjust for multiple testing, we considered $p<.01$ as statistically significant.
Since the vascular apathy hypothesis is primarily based on findings in older persons, we post-hoc examined the influence of age on associations by introducing interaction factors between age and any of the vascular factors/diseases; and by repeating analyses in participants of 50 years of age and above and of 70 years of age and above.
Two sensitivity analyses were carried out. A first set of sensitivity analyses were conducted by not replacing missing data on covariates by their mean.

# Results

## Participants

The 663 study participants had a mean age of 46.5 years (range 18-86 years) and 66.5% were female. See table 1 for all other characteristics.

Of the 663 participants, 29 (4.4%) did not return the SAS and 19 (2.9%) did not answer to some of the questions on the SAS. Of the 615 participants that returned the SAS, 44.3% were apathetic (cut-off ≥14), the mean score was 18.4 (SD 5.4). Not returning the SAS or missing values on the SAS were not significantly related to gender, age, education, the identified mood factor, vascular risk factors or vascular diseases.

*Table 1. Characteristics of the study population (N=663)*

| **Characteristics:** | | **Values** |
|---|---|---|
| *Demographics:* | | |
| - Age (years) | mean (SD) | 46.5 (16.1) |
| - Female sex | n (%) | 441 (66.5) |
| - Level of education: | | |
| - Basic | n (%) | 55 (8.3) |
| - Intermediate | n (%) | 407 (61.4) |
| - High | n (%) | 201 (30.3) |
| *Psychopathology:* | | |
| - SAS | mean (SD) | 18,4 (5.4) |
| - IDS-SR | mean (SD) | 16,0 (10.7) |
| - Use of benzodiazepines | n (%) | 83 (12.5) |
| - Use of antipsychotics | n (%) | 27 (4.1) |
| - Use of antidepressants | n (%) | 224 (33.8) |
| *Vascular risk factors & health:* | | |
| - Smoking | n (%) | 182 (27.5) |
| - lBMI | mean (SD) | 26.8 (5.0) |
| - Systolic blood pressure | mean (SD) | 135.7 (18.4) |
| - Diastolic blood pressure | mean (SD) | 79.5 (9.6) |
| - Ankle brachial index | mean (SD) | 1.2 (0.1) |
| - Diabetes mellitus | n (%) | 29 (4.4) |
| - Cardiac disease | n (%) | 57 (8.6) |
| - Cerebrovascular accident | n (%) | 22 (3.3) |
| - Handgrip strength | mean (SD) | 32.0 (16.9) |

*Abbreviations*: SAS, Starkstein apathy scale; IDS-SR, Inventory of Depressive Symptomatology-Self Report

## Multivariate regression analyses

### Primary analyses

The SAS sum score was not significantly associated with smoking, body mass index, blood pressure, ankle brachial index, diabetes mellitus, cardiac disease, or stroke, when age, sex, level of education, psychotropic drug use, physical performance, and residual mood symptoms were corrected for (see Table 2).

### Sensitivity analyses

Furthermore, neither amotivation nor loss of initiative was associated with any of the vascular risk factors, or vascular diseases, in the fully corrected model (see Table 3). We identified no significant interactions between age and the vascular factors under study on their association with the SAS sum score or any of the apathy factors. Moreover, the results were the same when the analyses were repeated in participants aged ≥50 years as well as when repeated in participants aged ≥70 years.

Nor did analyzing the association between vascular risk factors and diseases with the SAS sum score or the apathy factors identified, now adjusted for the mood subscale of the IDS or for the IDS sum score, result in any significant association. Other sensitivity analyses (i.e., not replacing missing covariates with their mean) yielded the same results.

*Table 2. Association of vascular factors with the Starkstein Apathy Scale sum score by multiple regression**

| | | Total apathy scale score | |
|---|---|---|---|
| **Vascular risk factors:** | *Beta* | *B (95% C.I.)* | *P-value* |
| - Smoking | 0.07 | 0.85 (-0.09-1.80) | 0.08 |
| - Body mass index | 0.03 | 0.04 (-0.04-0.12) | 0.36 |
| - Systolic blood pressure | -0.03 | -0.01 (-0.04-0.02) | 0.49 |
| - Diastolic blood pressure | 0.00 | 0.00 (-0.05-0.05) | 0.99 |
| - Ankle brachial index | 0.02 | 0.86 (-2.25-3.97) | 0.59 |
| - Diabetes mellitus | 0.04 | 1.20 (-0.88-3.27) | 0.26 |
| **Vascular disease:** | *Beta* | *B (95% C.I.)* | *P-value* |
| - Cardiac disease | 0.03 | 0.68 (-0.92-2.28) | 0.40 |
| - Stroke | 0.02 | 0.63 (-1.75-3.00) | 0.61 |

* All results have been corrected for age, sex, level of education, mood, physical performance, use of antidepressants, antipsychotics, and benzodiazepines
*Abbreviations*: C.I., Confidence Intervals.

*Table 3. Association of vascular factors with amotivation and loss of initiative by multiple linear regression**

| | Amotivation | | | Loss of initiative | | |
|---|---|---|---|---|---|---|
| **Vascular risk factors:** | *Beta* | *B (95% C.I.)* | *P-value* | *Beta* | *B (95% C.I.)* | *P-value* |
| - Smoking | 0.03 | 0.06 (-0.10-0.22) | 0.48 | 0.08 | 0.17 (0.00-0.33) | 0.04 |
| - Body mass index | 0.08 | 0.02 (0.01-0.03) | 0.04 | -0.07 | -0.01 (-0.03-0.00) | 0.08 |
| - Systolic blood pressure | 0.01 | 0.00 (-0.04-0.05) | 0.98 | -0.07 | -0.00 (-0.01-0.00) | 0.10 |
| - Diastolic blood pressure | 0.02 | 0.00 (-0.05-0.10) | 0.56 | -0.06 | -0.01 (-0.01-0.00) | 0.12 |
| - Ankle brachial Index | 0.03 | 0.19 (-0.34-0.72) | 0.49 | 0.01 | 0.07 (-0.47-0.62) | 0.79 |
| - Diabetes mellitus | 0.07 | 0.34 (-0.01-0.69) | 0.06 | -0.01 | -0.00 (-0.39-0.34) | 0.89 |
| **Vascular disease:** | *Beta* | *B (95% C.I.)* | *P-value* | *Beta* | *B (95% C.I.)* | *P-value* |
| - Cardiac disease | 0.01 | 0.05 (-0.23-0.32) | 0.74 | 0.04 | 0.13 (-0.15-0.41) | 0.38 |
| - Stroke | 0.01 | 0.05 (-0.36-0.45) | 0.83 | 0.02 | 0.10 (-0.32-0.51) | 0.66 |

* All results have been corrected for age, sex, level of education, mood, physical performance, use of antidepressants, antipsychotics, and benzodiazepines
*Abbreviations*: C.I., Confidence Intervals.



## Discussion

In contrast to our hypothesis, we did not find any association between vascular risk factors or vascular diseases and apathy among people with remitted depression. This finding is in line with a smaller study on apathy in 50 patients who had received electric convulsion therapy (ECT) for severe late-life depression [38]. In this study, apathy persisted in 52% of these patients while their depressive disorder had remitted. Nonetheless, the remaining apathy was also not related to MRI-based white matter hyperintensities, vascular disease, diabetes mellitus, or smoking. Collectively, these results imply that remaining apathy in remitted depression is not related to vascular disease and to structural cerebrovascular damage of the fronto-striatal circuitries.

How can we explain the lack of any association between vascular risk factors and diseases with remaining apathy after depression? The most likely hypothesis in our opinion stems from a heterogeneous pathophysiology of apathy in combination with the specific selection of depressed patients. Just like any other psychiatric disorder, apathy is a behavioral syndrome defined at the phenomenological level. Most studies on the pathophysiology of apathy have been conducted in patients with neurodegenerative disorders, i.e. Alzheimer's disease or Parkinson's disease [39 40], or overt cerebrovascular disease like stroke patients [41 42]. In these patients, fronto-striatal circuitries are structurally compromised. A recent meta-analysis that pooled data of studies in populations of Alzheimer's disease patients, stroke patients and healthy elderly persons, found an odds ratio of 1.41 (95% C.I. 1.05-1.89) for apathy in those with a high level of white matter hyperintensities, which is a biomarker for cerebral small vessel disease [43]. Based on these findings one might

hypothesize that vascular risk factors and (cerebro)vascular disease would also have been associated with apathy in remitted depression. Nonetheless, patients with depression are a selection of the general population and the pathophysiology of apathy in these patients might differ from that in the general population. Possibly, in depressed populations apathy might be related to either disturbances in functional connectivity patterns between brain areas [44] and/or psychosocial circumstances (e.g., non-challenging environments) [45]. In our population, the contribution of structural cerebrovascular damage to the origin of apathy might be too small, especially as we have only indirectly assessed the cerebrovascular disease burden by its risk factors and peripheral diseases. Nonetheless, a recent study on severe late-life depression also found much overlap between depression and apathy, but again, both were not related with vascular hyperintensities identified by brain imaging [46]. Therefore, we accordingly wonder whether apathy in remitted depression should not be regarded as a residual symptom of the depression itself. Especially as loss of interest and psychomotor changes are among the residual symptoms most often seen after depression and related to impairment in psychosocial functioning, such as maintaining work and a family life [47 48 8].

A diagnostic dilemma, -which warrants future research-, arises here. Should a clinician treat apathy as a residual symptom of successfully treated depression [49], because in general such symptoms are a risk factor for relapse [50 51]. Or should a clinician consider apathy as a syndrome unrelated to depression and in need of targeted treatment?

## Methodological considerations

Although in essence a cross sectional design, a strength of our study is that the diagnosis of remitted depression was established prospectively. Another strength is the sample size and wide age range of the study population. Most studies on vascular disease include older populations and in studies of younger populations cardiovascular diseases are often disregarded. Finally, we adjusted for the use of antidepressants, antipsychotics and benzodiazepines which might confound results due to their sedative or dopaminergic modulating properties [52 53 54] and ruled out that apathy might be due to functional limitations by adjusting for handgrip strength as an indicator of fitness [37].
In our attempt to identify determinants of apathy, we tried to avoid confounding due to overlap between apathy scales and depression scales [55]. Based on a principal factor analysis on the items of the Starkstein Apathy Scale (SAS) as well as the Inventory of Depressive Symptomatology (IDS) we distinguished two dimensions of apathy, i.e., amotivation and loss of initiative. Nonetheless, a factor analysis combining items from different scales, may artificially result in separate dimensions. This issue cannot be discarded as both apathy factors only included items of the SAS and the 'pure mood' factor only items of the IDS. Nonetheless, dichotomizing all items, thereby minimizing the impact of different response tendencies between the items of both scales, resulted in the same factor solution. Since specific items of the SAS and IDS did not load on the factors of interest, the present approach might still be a valuable addition to the use of the SAS sum score and an improvement over the use of the IDS sum score. Moreover, a sensitivity analysis using the IDS sum score did not change our results.

A second limitation is the duration of follow-up at 6 years. This timepoint of our evaluation was purely pragmatic as this follow-up assessment has included the SAS in both cohort studies. The lack of data on the participants lost to follow-up, might have obscured some small correlations as dropout might have been related to a more severe vascular disease status. Furthermore, since the SAS was administered only once in NESDA, our evaluation was merely cross-sectional in nature and we were unable to track the course of apathy in relation to vascular factors and mood. Another limitation is the use of a self-report scale for apathy, since respondents with minimal cognitive impairment (MCI) or dementia tend to report lower apathy levels than peers without these cognitive impairments, probably due to less cognitive insight [56]. Although dementia was an exclusion criterion for participation in this study, some participants could have been suffering from MCI, which could have influenced the association between the apathy sum score and vascular risk factors or vascular diseases.

## Conclusion

The results from this study do not support the hypothesis that apathy in remitted depression is linked with cerebrovascular damage of the fronto-striatal circuitries. Since apathy is highly frequent in remitted depression, its etiological basis warrants more attention in future research. This is especially relevant as apathy is related to a lower quality of life [57], functional decline [58] and a poorer prognosis for a variety of health outcomes [59], irrespective of its underlying pathophysiology.



## Fundings:

**NESDA:** The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum)

**NESDO:** The infrastructure for NESDO is funded through the Fonds NutsOhra, Stichting tot Steun VCVGZ, NARSAD The Brain and Behaviour Research Fund, and the participating universities and mental health care organizations (VU University Medical Center, Leiden University Medical Center, University Medical Center Groningen, Radboud University Nijmegen Medical Center, and GGZ inGeest, GGNet, GGZ Nijmegen, GGZ Rivierduinen, Lentis, and Parnassia)

## References


1. Robert P, Lanctôt KL, Agüera-Ortiz L, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *Eur Psychiatry*. 2018;54:71-76. doi:10.1016/J.EURPSY.2018.07.008
2. Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry*. 2011;26(2):158-165. doi:10.1002/GPS.2508
3. Groeneweg-Koolhoven I, Comijs H, Naarding P, de Waal M, van der Mast R. Apathy in Older Persons With Depression: Course and Predictors: The NESDO Study. *J Geriatr Psychiatry Neurol*. 2016;29(4):178-186.
4. Rothschild AJ, Raskin J, Wang CN, Marangell LB FMT relationship between change in apathy and changes in cognition and functional outcomes in currently non-depressed S patients with major depressive disorder. CP 2014 J-10. doi: 10. 1016/j. comppsych. 2013. 08. 00. The relationship between change in apathy and changes in cognition and functional outcomes in currently non-depressed SSRI-treated patients with major depressive disorder. *Compr Psychiatry*. 2014;55(1):1-10.
5. Nierenberg AA. Residual symptoms in depression: prevalence and impact. *J Clin Psychiatry*. 2015;76(11):e1480.
6. Hellström LC, Eplov LF, Nordentoft M, Ostergaard SD, Bech P. The Diagnostic Apathia Scale predicts the ability to return to work following depression or anxiety. *Acta Neuropsychiatr*. 2014;26(6):364-371. doi:10.1017/NEU.2014.23
7. Gastó C, Navarro V, Catalán R, Portella M, Marcos T. Residual symptoms in elderly major depression remitters. *Acta Psychiatr Scand*. 2003;108(1):15-19.
8. Vieta E, Sánchez-Moreno J, Lahuerta J, Zaragoza S. Subsyndromal depressive symptoms in patients with bipolar and unipolar disorder during clinical remission. *J Affect Disord*. 2008;107(1-3):169-174. doi:10.1016/j.jad.2007.08.007
9. Fahed M, Steffens DC. Apathy: Neurobiology, Assessment and Treatment. *Clin Psychopharmacol Neurosci*. 2021;19(2):181-189. doi:10.9758/CPN.2021.19.2.181
10. Verhoeven F, Wardenaar K, Ruhé H, Conradi H, de Jonge P. Seeing the signs: Using the course of residual depressive symptomatology to predict patterns of relapse and recurrence of major depressive disorder. *Depress Anxiety*. 2018;35(2):148-159.
11. Fava GA, Ruini C, Belaise C. The concept of recovery in major depression. *Psychol Med*. 2007;37(3):307-317. doi:10.1017/S0033291706008981
12. Calabrese JR, Fava M, Garibaldi G, et al. Methodological approaches and magnitude of the clinical unmet need associated with amotivation in mood disorders. *J Affect Disord*. 2014;168:439-451. doi:10.1016/j.jad.2014.06.056

13. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: A transdiagnostic approach. *Nat Rev Neurosci*. 2018;19(8):470-484. doi:10.1038/s41583-018-0029-9

14. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex*. 2006;16(7):916-928. doi:10.1093/CERCOR/BHJ043

15. Moretti R, Signori R. Neural correlates for apathy: Frontal-prefrontal and parietal cortical- subcortical circuits. *Front Aging Neurosci*. 2016;8(DEC). doi:10.3389/fnagi.2016.00289

16. Theleritis C, Politis A, Siarkos K, Lyketsos CG. A review of neuroimaging findings of apathy in Alzheimer's disease. *Int Psychogeriatrics*. 2014;26(2):195-207. doi:10.1017/S1041610213001725

17. Thobois S, Prange S, Sgambato-Faure V, Tremblay L, Broussolle E. Imaging the Etiology of Apathy, Anxiety, and Depression in Parkinson's Disease: Implication for Treatment. *Curr Neurol Neurosci Rep*. 2017;17(10). doi:10.1007/s11910-017-0788-0

18. Alexopoulos GS, Hoptman MJ, Yuen G, et al. Functional connectivity in apathy of late-life depression: A preliminary study. *J Affect Disord*. 2013;149(1-3):398-405. doi:10.1016/J.JAD.2012.11.023

19. Pimontel MA, Kanellopoulos D, Gunning FM. Neuroanatomical Abnormalities in Older Depressed Adults With Apathy: A Systematic Review. *J Geriatr Psychiatry Neurol*. 2020;33(5):289-303. doi:10.1177/0891988719882100

20. Yuen GS, Gunning FM, Woods E, Klimstra SA, Hoptman MJ, Alexopoulos GS. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *J Affect Disord*. 2014;166:179-186. doi:10.1016/j.jad.2014.05.008

21. Pimontel MA, Solomonov N, Oberlin L, et al. Cortical Thickness of the Salience Network and Change in Apathy Following Antidepressant Treatment for Late-Life Depression. Published online 2021. doi:10.1016/j.jagp.2020.06.007

22. Ligthart SA, Richard E, Fransen NL, et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69(6):636-642. doi:10.1001/archgenpsychiatry.2011.1858

23. Marijnissen RM, Bus BAA, Schoevers RA, et al. Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry*. 2014;22(8):801-810. doi:10.1016/j.jagp.2013.01.001

24. Wouts L, Kessel M van, Beekman ATF, Marijnissen RM, Voshaar RCO. Empirical support for the vascular apathy hypothesis: A structured review. *Int J Geriatr Psychiatry*. 2020;35(1):3-11. doi:10.1002/GPS.5217

25. Penninx BWJH, Eikelenboom M, Giltay EJ, et al. Cohort profile of the longitudinal Netherlands Study of Depression and Anxiety (NESDA) on etiology, course and consequences of depressive and anxiety disorders. *J Affect Disord*. 2021;287:69-77. doi:10.1016/J.JAD.2021.03.026

26. 26. Penninx BWJH, Beekman ATF, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): Rationale, objectives and methods. *Int J Methods Psychiatr Res*. 2008;17(3):121-140. doi:10.1002/mpr.256

27. Comijs HC, Van Marwijk HW, Van Der Mast RC, et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res Notes*. 2011;4. doi:10.1186/1756-0500-4-524

28. Kessler RC, Üstün BB. The World Mental Health (WMH) Survey Initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res*. 2004;13(2):93-117. doi:10.1002/mpr.168

29. Andrews G, Peters L. The psychometric properties of the Composite International Diagnostic Interview. *Soc Psychiatry Psychiatr Epidemiol*. 1998;33(2):80-88. doi:10.1007/s001270050026

30. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4(2):134-139. doi:10.1176/jnp.4.2.134

31. Weiser M, Garibaldi G. Quantifying motivational deficits and apathy: A review of the literature. *Eur Neuropsychopharmacol*. 2015;25(8):1060-1081. doi:10.1016/j.euroneuro.2014.08.018

32. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, clinician rating (IDS-C) and self-report (IDS-SR), and the Quick Inventory Depressive Symptomatology, clinician rating (QIDS-C) and self-report (QIDS-SR) in public sector patients with mood disorders: A psychometric evaluation. *Psychol Med*. 2004;34(1):73-82. doi:10.1017/S0033291703001107

33. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The inventory of depressive symptomatology (IDS): Psychometric properties. *Psychol Med*. 1996;26(3):477-486. doi:10.1017/s0033291700035558

34. Comijs HC, van Marwijk HW, van der Mast RC, et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res Notes*. 2011;4:524. doi:10.1186/1756-0500-4-524

35. Casey S, Lanting S, Oldmeadow C, Chuter V. The reliability of the ankle brachial index: A systematic review. *J Foot Ankle Res*. 2019;12(1). doi:10.1186/s13047-019-0350-1

36. Li Z, Liu J. Coexistence of low ankle-brachial index and intracranial atherosclerosis? *Int Angiol*. 2014;33(5):461-465. Accessed April 15, 2021. https://pubmed-ncbi-nlm-nih-gov.proxy-ub.rug.nl/25294288/

37. Kriegsman DMW, Penninx BWJH, Van Eijk JTM, Boeke AJP, Deeg DJH. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol*. 1996;49(12):1407-1417. doi:10.1016/S0895-4356(96)00274-0

38. Jakobsen LH, Rask IK, Kondrup J. Validation of handgrip strength and endurance as a measure of physical function and quality of life in healthy subjects and patients. *Nutrition*. 2010;26(5):542-550. doi:10.1016/j.nut.2009.06.015

39. Carlier A, van Exel E, Dols A, et al. The course of apathy in late-life depression treated with electroconvulsive therapy; a prospective cohort study. *Int J Geriatr Psychiatry*. 2018;33(9):1253-1259. doi:10.1002/gps.4917

40. Bock MA, Bahorik A, Brenowitz WD, Yaffe K. Apathy and risk of probable incident dementia among community-dwelling older adults. *Neurology*. 2020;95(24):e3280-e3287. doi:10.1212/WNL.0000000000010951

41. Lavretsky H, Ballmaier M, Pham D, Toga A, Kumar A. Neuroanatomical characteristics of geriatric apathy and depression: A magnetic resonance imaging study. *Am J Geriatr Psychiatry*. 2007;15(5):386-394. doi:10.1097/JGP.0b013e3180325a16

42. Douven E, Köhler S, Rodriguez MMF, Staals J, Verhey FRJ, Aalten P. Imaging Markers of Post-Stroke Depression and Apathy: a Systematic Review and Meta-Analysis. *Neuropsychol Rev*. 2017;27(3):202-219. doi:10.1007/S11065-017-9356-2

43. Tay J, Lisiecka-Ford DM, Hollocks MJ, et al. Network neuroscience of apathy in cerebrovascular disease. *Prog Neurobiol*. 2020;188. doi:10.1016/j.pneurobio.2020.101785

## Supplemental information

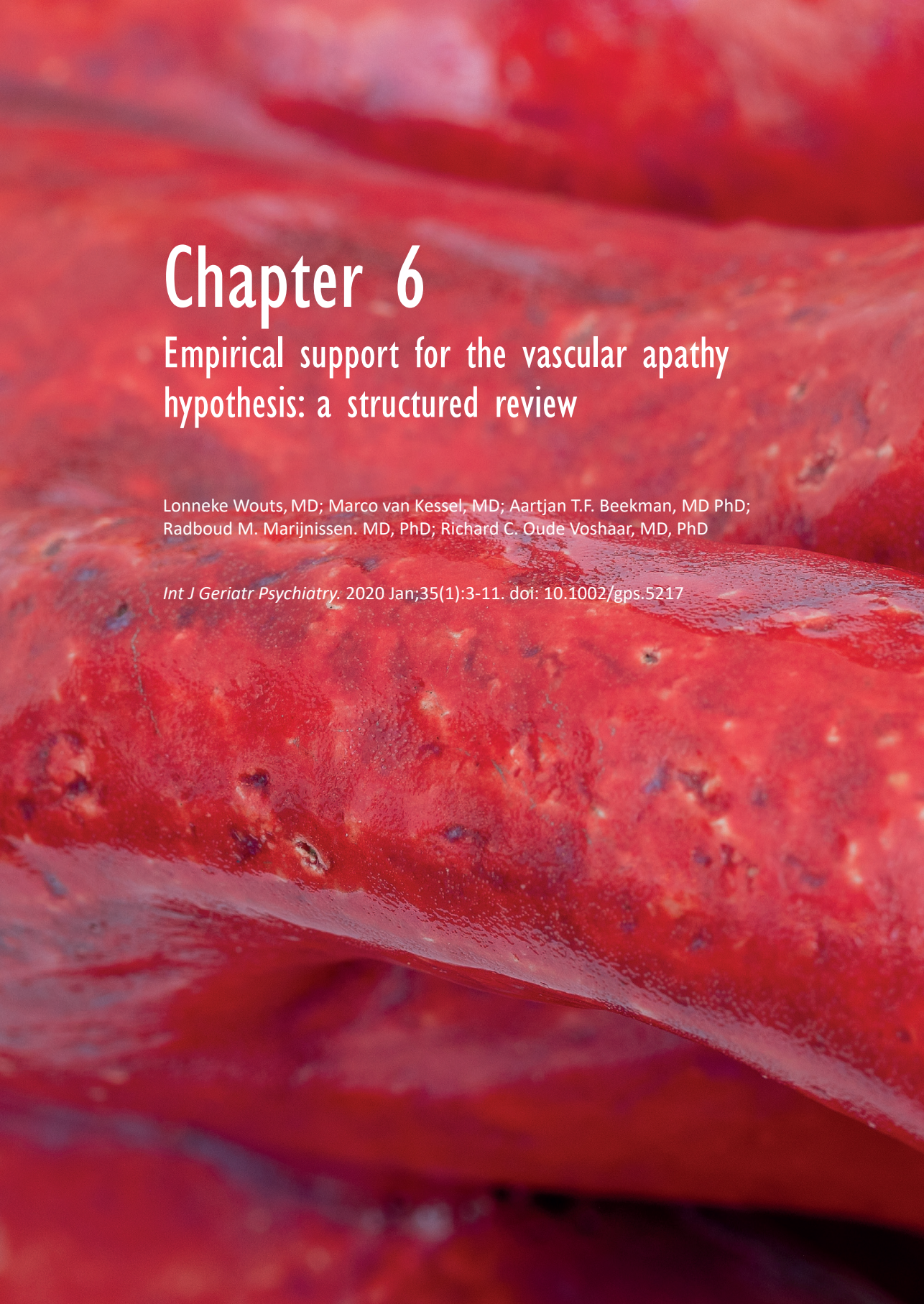
Eigenvalues, % of variance and rotated factor pattern resulting from the factor analysis

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| | | Mood | Apathy -Amotivation | Mood variation | Somatic affective symptoms | Apathy -Loss of initiative | Sleep disturbance | Appetite-weight | |
| | Statistics: | | | | | | | | |
| | Eigenvalue | 12,43 | 2,83 | 2,22 | 1,78 | 1,53 | 1,42 | 1,17 | 1,11 |
| | % of Variance | 28,24 | 6,43 | 5,04 | 4,04 | 3,48 | 3,22 | 2,66 | 2,53 |
| | Starkstein Apathy Scale (SAS) | | | | | | | | |
| 1 | Are you interested in learning new things? | -,04 | ,73 | ,01 | ,03 | -,03 | -,13 | ,03 | -,04 |
| 2 | Does anything interest you? | ,00 | ,72 | -,03 | -,00 | -,03 | -,09 | -,00 | -,08 |
| 3 | Are you concerned about your condition? | ,06 | ,10 | ,03 | -,61 | -,22 | ,17 | ,14 | -,14 |
| 4 | Do you put much effort into things? | -,03 | ,74 | ,05 | -,06 | ,09 | ,12 | -,00 | ,03 |
| 5 | Are you always looking for something to do? | -,09 | ,76 | -,02 | -,04 | -,05 | ,07 | -,03 | ,09 |
| 6 | Do you have plans and goals for the future? | ,04 | ,72 | -,01 | ,00 | ,06 | -,09 | -,01 | -,00 |
| 7 | Do you have motivation? | ,15 | ,71 | -,01 | ,01 | ,12 | ,06 | ,02 | ,05 |

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| | | Mood | Apathy -Amotivation | Mood variation | Somatic affective symptoms | Apathy -Loss of initiative | Sleep disturbance | Appetite-weight | |
| 8 | Do you have the energy for daily activities? | ,15 | ,31 | ,01 | ,46 | ,07 | ,13 | ,11 | -,02 |
| 9 | Does someone have to tell you what to do each day? | -,03 | -,05 | -,02 | -,03 | ,70 | ,08 | ,08 | ,14 |
| 10 | Are you indifferent to things? | -,02 | ,01 | ,04 | -,09 | ,68 | -,17 | ,01 | -,30 |
| 11 | Are you unconcerned with many things? | ,04 | ,07 | ,02 | ,05 | ,67 | -,10 | -,01 | -,22 |
| 12 | Do you need a push to get started on things? | ,00 | ,12 | ,04 | ,14 | ,68 | ,09 | ,00 | ,16 |
| 13 | Are you neither happy nor sad, just in between? | ,18 | ,06 | ,07 | ,19 | ,45 | -,00 | -,07 | ,16 |
| 14 | Would you consider yourself apathetic? | ,20 | ,10 | ,01 | -,08 | ,54 | -,02 | ,03 | -,04 |
| | Inventory of Depressive Symptoms (IDS) | | | | | | | | |
| 1 | Falling asleep | ,08 | ,07 | ,08 | ,20 | ,02 | -,44 | ,00 | ,08 |
| 2 | Sleep during the night | -,06 | ,05 | ,02 | ,17 | -,02 | -,60 | ,00 | -,13 |
| 3 | Waking up too early | ,06 | -,01 | ,01 | -,01 | ,08 | -,69 | ,07 | ,01 |
| 4 | Sleeping too much | -,01 | ,03 | ,04 | ,42 | ,05 | ,44 | -,02 | -,38 |
| 5 | Feeling sad | ,77 | ,07 | ,06 | ,02 | ,09 | ,00 | -,06 | ,05 |

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| | | Mood | Apathy -Amotivation | Mood variation | Somatic affective symptoms | Apathy -Loss of initiative | Sleep disturbance | Appetite-weight | |
| 6 | Feeling irritable | ,63 | ,00 | ,03 | ,09 | ,02 | ,03 | ,08 | ,22 |
| 7 | Feeling anxious or tense | ,61 | ,03 | ,08 | ,16 | ,02 | -,04 | ,03 | ,30 |
| 8 | Response of your mood to good or desired events | ,66 | ,05 | -,04 | -,12 | ,01 | -,15 | -,07 | -,31 |
| 9a | Mood in relation to the time of day | -,03 | ,01 | ,96 | -,04 | -,04 | ,03 | -,04 | -,01 |
| 9b | Mood typically worse in morning, afternoon or night? | -,03 | -,04 | ,98 | -,05 | -,01 | -,02 | ,01 | ,02 |
| 9c | Is your mood variation attributed to the environment? | -,05 | -,03 | 1,00 | -,05 | ,00 | -,01 | -,02 | -,01 |
| 10 | The quality of your mood | ,67 | ,04 | ,06 | -,02 | ,06 | -,06 | -,01 | ,00 |
| 11/12 | Change in appetite | ,09 | -,00 | ,02 | ,05 | ,04 | ,06 | ,70 | ,05 |
| 13/14 | Weight change (within the last two weeks) | -,15 | ,00 | -,01 | -,03 | ,02 | -,09 | ,85 | -,04 |
| 15 | Concentration/decision making | ,52 | ,07 | ,03 | ,05 | ,13 | ,01 | ,21 | -,00 |
| 16 | View of myself | ,61 | ,05 | ,04 | -,03 | ,10 | ,08 | ,08 | ,09 |
| 17 | View of my future | ,53 | ,17 | ,06 | ,14 | ,08 | -,12 | -,07 | -,01 |
| 18 | Thoughts of death or suicide | ,50 | -,02 | ,06 | ,05 | ,06 | -,03 | -,10 | -,10 |
| 19 | General interest | ,63 | ,08 | ,01 | ,03 | ,05 | ,00 | ,09 | -,26 |

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| | | Mood | Apathy -Amotivation | Mood variation | Somatic affective symptoms | Apathy -Loss of initiative | Sleep disturbance | Appetite-weight | |
| 20 | Energy level | ,34 | ,04 | ,03 | ,44 | ,03 | ,05 | ,18 | -,22 |
| 21 | Capacity for pleasure or enjoyment | ,75 | ,09 | ,02 | -,02 | ,02 | -,04 | ,00 | -,24 |
| 22 | Interest in sex | ,19 | ,14 | ,04 | ,24 | ,02 | -,16 | ,05 | -,34 |
| 23 | Feeling slowed down | ,46 | ,02 | ,05 | ,03 | ,05 | -,07 | ,21 | -,23 |
| 24 | Feeling restless | ,44 | -,06 | ,01 | ,07 | ,04 | -,14 | ,17 | ,21 |
| 25 | Aches and pains | ,01 | ,05 | ,04 | ,65 | -,03 | -,11 | ,11 | -,01 |
| 26 | Other bodily symptoms | ,17 | ,08 | ,04 | ,49 | -,03 | -,21 | ,05 | ,08 |
| 27 | Panic/phobic symptoms | ,39 | ,05 | ,05 | ,27 | -,08 | -,04 | -,00 | ,31 |
| 28 | Constipation/diarrhea | ,00 | ,00 | ,08 | ,49 | -,02 | -,04 | ,16 | -,07 |
| 29 | Interpersonal sensitivity | ,58 | -,04 | ,06 | ,06 | ,06 | ,13 | ,11 | ,18 |
| 30 | Leaden paralysis/physical energy | ,29 | ,06 | ,04 | ,54 | ,03 | ,07 | ,15 | -,10 |

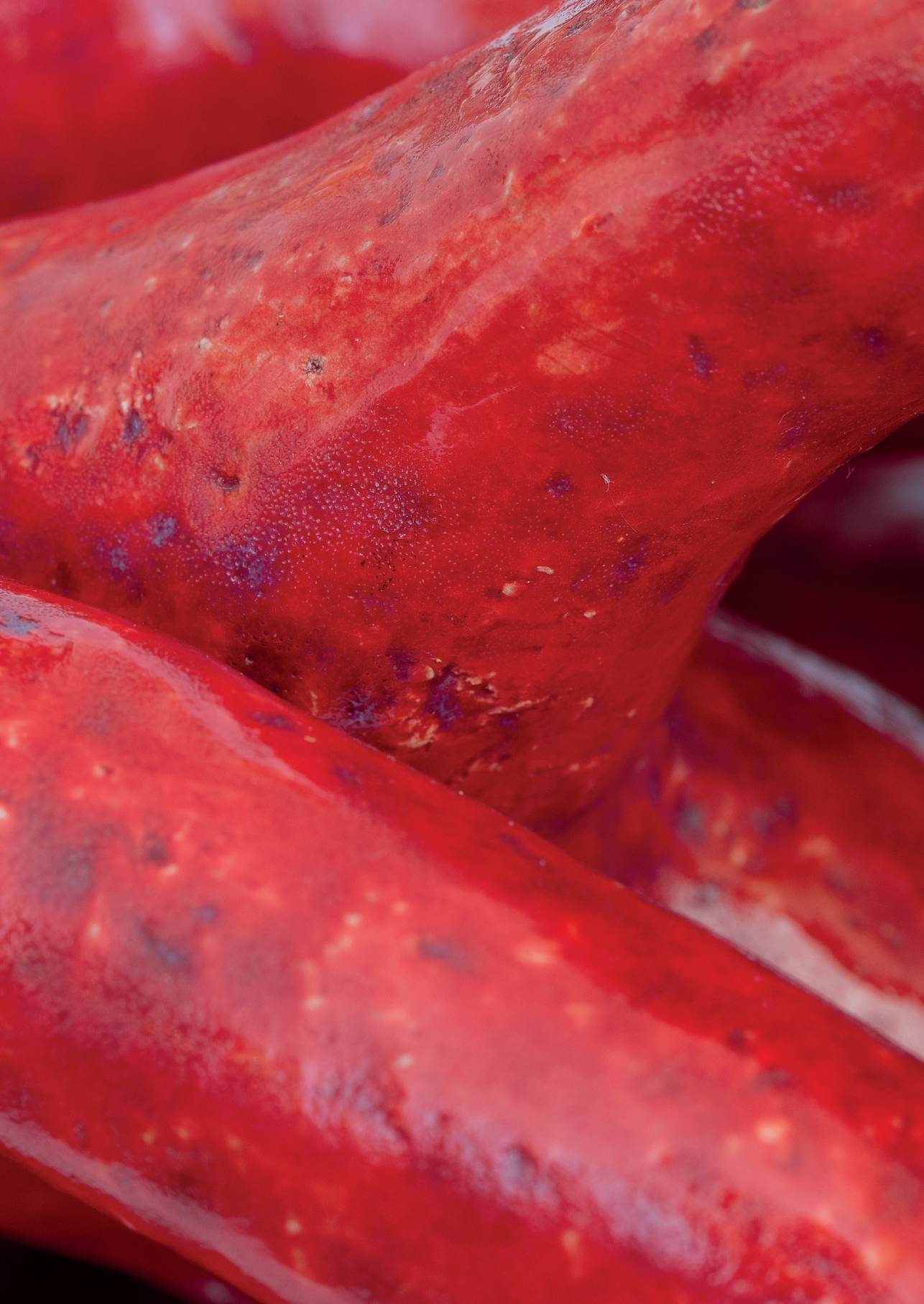


# Chapter 6

## Empirical support for the vascular apathy hypothesis: a structured review

Lonneke Wouts, MD; Marco van Kessel, MD; Aartjan T.F. Beekman, MD PhD; Radboud M. Marijnissen. MD, PhD; Richard C. Oude Voshaar, MD, PhD

*Int J Geriatr Psychiatry.* 2020 Jan;35(1):3-11. doi: 10.1002/gps.5217



# Abstract

## Objectives

A systematic review of the relationship between subclinical small vessel disease (SSVD) in the general population and apathy to examine the hypothesis that apathy has a vascular basis.

## Methods

We searched for studies on associations between apathy and SSVD, operationalized as white matter hyperintensities (WMH) or white matter diffusivity changes, lacunar infarcts, cerebral microbleeds, decreasing cortical thickness, and perivascular spaces, while also peripheral proxies for SSVD were considered, operationalized as ankle brachial pressure index (ABI), intima media thickness, arterial stiffness, cardio-femoral pulse wave velocity, hypertension or cardiovascular disease. Only eligible retrospective and prospective observational studies conducted in the general population were included.

## Results

The 14 studies eligible for review examined the associations between apathy and hypertension (3), ABI (1), arterial stiffness (1), cardiovascular disease (2), WMH (3), white matter diffusivity (2), cerebral microbleeds (1), or cortical thickness (3). Arterial stiffness and white matter diffusivity were not related to apathy, while the associations with cortical thickness were contradictory. Cross-sectional studies in the general population did find evidence of apathy being associated with WMH, CM, cardiovascular disease, hypertension and ABI and cardiovascular disease was prospectively associated with apathy. The methodologies of the studies reviewed were too heterogeneous to perform meta-analyses.

## Conclusions

Although more prospective evidence is needed and vascular depression needs to be controlled for, cardiovascular disease, hypertension and ABI as proxies for SSVD, and WMH and cerebral microbleeds as direct measures of SSVD have been found to be associated with apathy in the general population, supporting the hypothesis of vascular apathy.

# Introduction

Apathy, or diminished motivation, has traditionally been regarded as a symptom of psychiatric and neurological disorders, such as major depressive disorder [1] and Parkinson's disease [2]. Apathy has increasingly come to be regarded as an independent syndrome for which diagnostic criteria have been proposed in a consensus paper [3 4]. With its prevalence in the general population (≥50 years) being estimated at 23.7% [5], the impact of apathy on both individuals and the society is extensive. The apathy syndrome negatively affects motivational decision making [6] and is associated with functional decline [5], reduced engagement in activities of daily living, and a poorer quality of life [7]. Understandably, apathy is very distressing for family and other caregivers [8].

The hypothesis of vascular apathy assumes a relationship between the generally widespread cerebrovascular damage caused by small vessel disease (SVD) and apathy [9 10]. Whether cerebrovascular damage due to small vessel disease, is associated with apathy, -even in the general population without prior knowledge of cerebrovascular damage-, is the main subject of this study.

Various brain circuits play a role in planning, motivation and, auto activation, among which are the frontal regions with their projections to prefrontal regions and the basal ganglia, the parietal regions, and the anterior cingulate [11]. The vascular apathy hypothesis then supposes that SVD can cause apathy by damaging these tracts. However, the relationship between vascular disease and apathy could well be bidirectional: a recent systematic review and meta-analysis showed that apathy increases the risk of myocardial infarction by 21 %, stroke by 37%, and even mortality by 47% [12]. In the populations evaluated, these risks might additionally or alternatively be raised due to the participants' adverse health behaviours and low adherence to treatment regimens for vascular disease [13 14 15]. Moreover, apathy and vascular disease might have a shared aetiology [16], while apathy could well be a marker of subclinical SVD (SSVD) [14].

Early evidence for the vascular apathy hypothesis was reported in studies in clinical samples with established cerebrovascular disease (e.g. vascular dementia and stroke), where apathy appeared related to the general effect (or severity) of cerebrovascular damage given that, associations with specific cerebral circuitries and regions were inconsistent [17 18]. Particularly the stroke subtype of SVD (lacunar infarcts and white matter hyperintensities) was found to be related to apathy in several other studies, independent of depression [19 20 21].

Indirect and also contradictory evidence came from research into late-life depression, where chronicity of late-life depression was found to be associated with the severity of the risk factors for cerebrovascular disease and apathy [22]. Still, although the presence of apathy was predicted by vascular factors in several elderly depressed populations [23], other studies found no such associations [24 12]. Moreover, depression itself could be related to vascular factors, as the so-called vascular depression hypothesis postulates [25] which

complicates the interpretation of findings pertaining to vascular apathy in depressed populations.

Other indirect evidence seems to support the existence of vascular apathy in that a negative interaction was observed between neuroticism and cerebrovascular risk factors in the prediction of depression, suggesting that apathy caused by SSVD might attenuate the depressogenic effect of neuroticism [10 26].

Obviously, more convincing and direct evidence of vascular apathy could come from research investigating the apathy-SSVD relationship in the general population, given that cerebral SVD develops from a subclinical condition, increasing the risk on overt cerebrovascular disease [27 28 29 30], where, although still subclinical, SSVD might cause subtle signs and symptoms, like mild disturbances in gait, cognitive functioning and mood [27],

The aim of the present systematic review is to examine all the evidence supporting an association between SSVD and apathy in the general population, while also considering findings of associations between proxies of SSVD and apathy.

# Methods

## Literature search process

All eligible articles were found using Ovid-all resources (which include the Cochrane Library, EMBASE, MEDLINE, and PSYCHINFO), limits: English, humans. The search terms were vascular apathy, and apathy combined with deep white matter hyperintensities (DWMH), white matter hyperintensities (WMH), cerebrovascular disease (not stroke) (CV disease), lacunar infarcts, cerebral microbleeds, cortical thickness, perivascular spaces, ankle brachial pressure index (ABI), intima media thickness (IMT), arterial stiffness, cardio-femoral pulse wave velocity (CFPWV), hypertension, cardiovascular disease and cerebrovascular risk factors (CVRF). Duplicates were removed.

The search was conducted on the 27th of June, 2018 by the first author (LW) and checked by the second author (MvK). Differences in findings were analyzed and discrepancies were discussed between both authors (LW and MvK) and when no consensus could be reached, a third author (RM) was asked to make the final judgment. Two more eligible articles were identified while preparing a speech on apathy using the search terms “apathy” and “dementia” [31 32]. On inspection these two studies also reported on the general population or populations with minimal cognitive impairment (MCI), which is why we included them in our review.

Articles were included when 1. apathy was assessed by any kind of relevant instrument; 2. SSVD was based on either neuroimaging, considered a direct measure of SSVD or peripheral measures of atherosclerosis, considered as proxies for SSVD; 3. studies reported on observational epidemiological research, and 4. were performed in the general

population. This implies that studies in broad patient groups or the general population including those with minimally cognitively impaired patients were included in the review. Studies were excluded i. when the language was not English and ii. when the studies concerned specific populations, such as post-stroke patients, patients with dementia (including vascular dementia), with Parkinson's disease or major depression.

## Study quality

The quality of the case control, cross-sectional and longitudinal studies selected for review was judged against specific criteria for design and methodology. We used an adapted version of the evaluation scale for cross-sectional (not case-control) studies originally developed by Kuijpers et al.[33] (online supplementary file 1). For case-control and longitudinal studies we used scales based on the Newcastle-Ottawa scale [34] (online supplementary file 2). Overall quality of a study was considered high when it attained at least 60% of the maximum score [35].

## Evaluation of the quality of apathy scales

The apathy evaluation scale (AES) and the apathy subscale of the neuropsychiatric inventory (NPI) were considered of high quality [36 37]. The 3 apathy items of the geriatric depression scale (GDS-3A) are validated by comparison with the apathy scale (sensitivity 69% and specificity 85% [29 38]). The apathy scale (an abbreviated version of the AES) and therefore also the apathy items of the GDS were not granted the highest quality status in our evaluation based on the review by Clarke et al., 2011 [37]. Clinician- or informant-based information was considered of higher quality than self-reported in the older population where individuals may have been suffering from MCI [39].

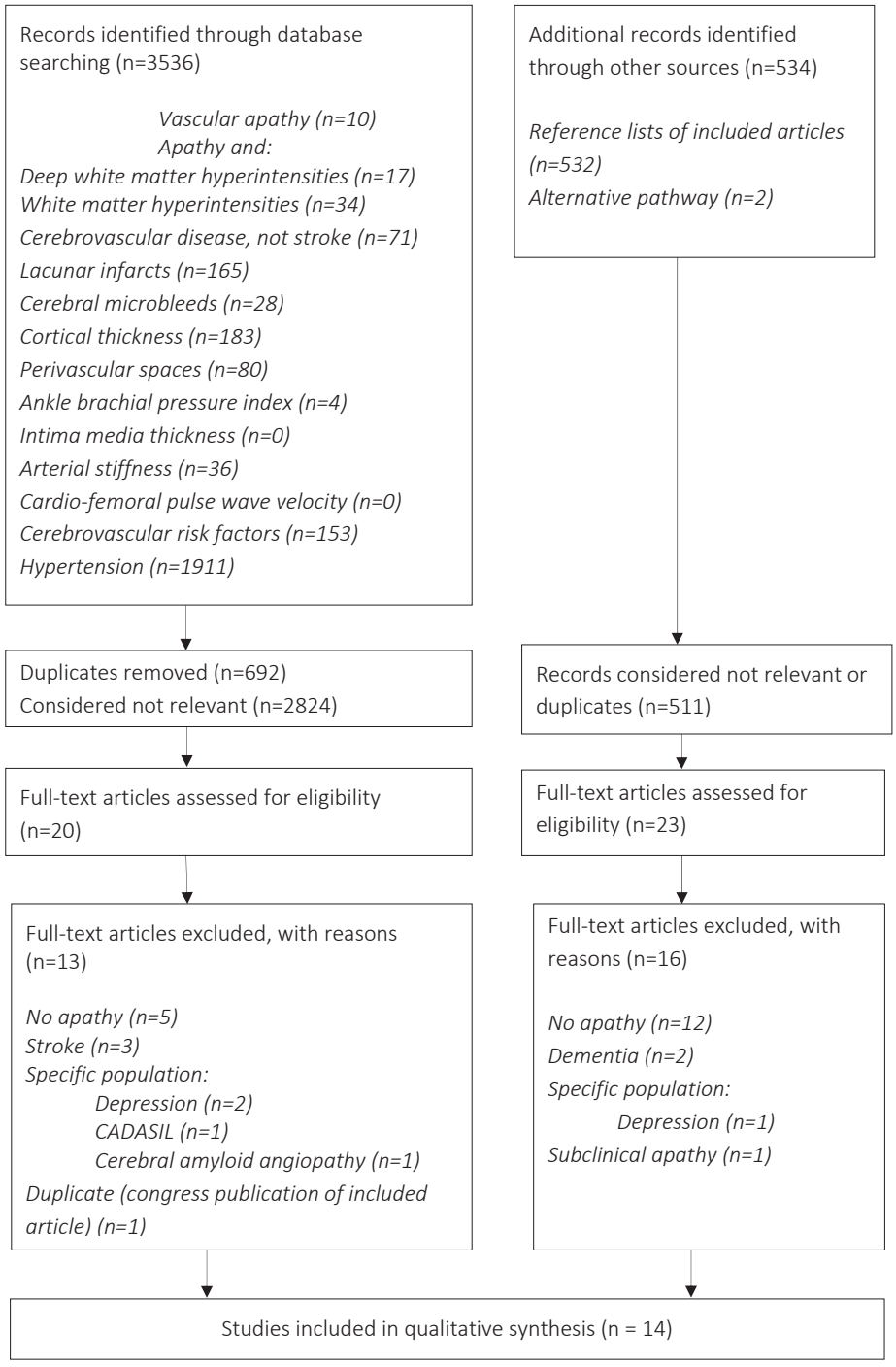
## Evaluation of the quality of SSVD assessment

SSVD on neuroimaging was operationalized as WMH, silent lacunar infarcts, cerebral microbleeds, or decreased cortical thickness on MRI scans [27]. Diffusion tensor imaging (DTI) studies the diffusivity of water molecules in white matter as a model of the connectivity of this tissue and its markers (fractional anisotropy and diffusivity) are associated with SVD [40].

Peripheral measures of atherosclerosis were operationalized as the ABI, IMT, and/or CFPWV. Although the ABI and CFPWV are measures of large artery atherosclerosis [41], we considered both measures proxies for SSVD as large artery and small vessel disease are closely related [42]. Cardiovascular disease was included as an SSVD proxy, since it can lead to haemodynamic changes affecting the small vessels [42]. Finally, being the strongest risk factor for SSVD, hypertension was also taken as an SSVD proxy [27 43].

Studies were awarded an extra point was if SSVD proxies were measured rather than mentioned in an interview or derived from information provided by general practitioners. Self-reported SSVD was categorized as "low quality".

*Figure 1. Flow chart of the inclusion of studies*



# Results

The results of the search strategy are shown in the flow chart depicted in Figure 1. No relevant studies published before 1990 were found. Of the 14 studies included in the review, one study reported on both peripheral proxies as well as direct measures of SSVD [30], four studies on peripheral proxies of SSVD only [9 29 43 44], and finally nine studies on direct measures of SSVD only [31 32 45 46 47 48 49 50 51].

## SSVD and apathy

In Table 1 the five studies that used peripheral proxies for SSVD are listed and details and results described. A meta-analysis of the results was not possible, because the research designs, SSVD proxies, and methods of ascertaining apathy that had been used differed too widely.

*Table 1. Studies with peripheral proxies for Subclinical small vessel disease*

| Author year | Population Study design Number of participants | Proxy for subclinical small vessel disease | Apathy instrument | Results | Quality |
|---|---|---|---|---|---|
| Van der Mast et al., 2008 | General population, >85 years, Longitudinal, 500 | CVP† | GDS-3A‡ | Mean number of CVP†: apathy 1.04 (0.11) versus no apathy 0.77 (0.05); p=0.02<br><br>CVP† and increase in apathy : 0.05 (0.02); p=0.007 | High (9/9) |
| Yao et al., 2009 | General population, Cross-sectional, 222 | Diastolic blood pressure | Apathy scale | Diastolic blood pressure: OR§ 1.055 (1.014-1.098); p=0.009 | High (10/16) |
| Suga-wara et al., 2011 | General population, Cross-sectional, 860 | ABI¶ | Apathy scale | ABI¶: beta-0.071 (t value-2.039); p<0.05<br><br>Systolic blood pressure: beta-0.056 (t value -1.420); p=0.156 | High (6/9) |
| Ligthart et al., 2012 | General population, Cross-sectional, 3534 | Cerebro-vascular risk factors | GDS-3A‡ | CVP† and apathy 1.28 (1.09-1.52); p=0.004<br><br>Systolic blood pressure is associated with apathy | High (12/16) |
| Van Sloten et al., 2016 | General population, Cross-sectional, 2058 | Arterial stiffness | GDS-3A‡ | Arterial stiffness: OR§ 1.07 (0.96-1.19) | High (11/16) |

Legend: † CVP: cardiovascular pathologies; ‡ GDS-3A: three apathy items of the geriatric depression scale; § OR: odds ratio; ¶ABI: ankle brachial index. High quality: ≥60% of the maximum score.

Three studies examined associations between hypertension and apathy [9 30 43], two of which found a significant link with systolic blood pressure [9 43], and the other with the diastolic (but not systolic) blood pressure [30]. This latter study [30] also examined the association between WMH and apathy by neuroimaging, of which the results are presented in section '*Neuroimaging and apathy*'.

In their large-scale study, Ligthart et al. [9] found an odds ratio (OR) of 1.28 in their participants with cardiovascular disease (1.09-1.52; p=0.004). The number of cardiovascular pathologies in another large and prospective study [29] was found to be associated with apathy at baseline and with incident apathy during follow-up.

Finally, ABI was associated with apathy [43], but arterial stiffness (CFPWV) was not [44].

## Neuroimaging and apathy

The ten studies using MRI or DTI are presented in Table 2.

Of the three studies examining the association between WMH and apathy, the two cross-sectional studies found a significant association [30 48] whereas the (smaller) case-control study did not [49]. Again, a meta-analysis and quantitative estimation of the WMH and apathy association was not possible, because of the large differences in the studies' research designs, the methods of ascertaining WMH (number or volume), and apathy scales used. It needs to be noted here, that with 4354 participants the study by Van Grool et al. [48] would have largely outweighed the findings of the other studies in any meta-analysis, since the other studies had much smaller samples.

Mean white matter diffusivity (MD) was associated with apathy in specific areas in the small-scale study by Cacciari et al. [45], but not in the study by Moonen et al. [50]. Other DTI measures (fractional anisotropy (FA); axial diffusivity (AD) and radial diffusivity (RD) were not associated with apathy [50].

Evaluating the data of 802 participants, Xu et al. [51] found the participants who had suffered a single cerebral microbleed to show significantly more apathy than participants without cerebral microbleeds.

Of the three studies examining looking at cortical thickness and apathy, two studies found an association between apathy and a reduced thickness of the temporal lobe [31 32]. No associations were reported for apathy and the entorhinal cortex, the orbitofrontal cortex, or the middle frontal gyrus [47], while no association or even an inverse association was found between apathy and the anterior cingulate [32 47]. However, in a model in which apathy was adjusted for depressive symptom severity, apathy was found to be associated with a more rapid reduction of the anterior cingulate cortex during follow-up [47].

# Discussion

## Main findings

The results of our review indeed support the hypothesis that SSVD is related with apathy. More specifically, as peripheral proxies for SSVD, hypertension and cardiovascular disease were consistently found to be associated with apathy [9 29 30 43]. With the only study examining ABI finding a significant association with apathy while another single study focusing on arterial stiffness did not [43 44], the results with respect to other peripheral measures of atherosclerosis were inconclusive. Apathy was, however, also linked to cerebral microbleeds [51] and WMH load [30 48]. SSVD was related to white matter diffusivity; however a direct association between white matter diffusivity and apathy has not been established yet [45 50]. The evidence on the relationship between cortical thickness and apathy is inconclusive [31 32 47].

## Hypertension, cardiovascular disease, white matter hyperintensities and apathy

Both systolic and diastolic blood pressure were associated with apathy [9 30 43], while associations between white matter hyperintensities and apathy (and cerebral microbleeds and apathy) were found in large-scale and high-quality studies [30 48 51]. Although Delrieu et al.[49] did not find any such evidence, their study may have been underpowered. Finally, cardiovascular disease was firmly associated with apathy, not only cross-sectionally but also longitudinally [9 29].

Although its aetiology is not fully understood, WMH reflects ischaemic arteriolosclerosis in the brain [27] and is related to congenital heart disease, hypertension, carotid blood flow, diabetes and cardiovascular health [52]. WMH may then be seen as consequence of chronic hypoperfusion as well as impaired cerebrovascular reactivity. Nonetheless, blood-brain-barrier leakage and myelin-remodeling problems could play a role [53]. The relation between hypertension, cardiovascular disease and WMH could be limited blood flow to the brain and/or arterial stiffness [52 53 54].

How SSVD can lead to apathy is not yet fully understood. Destruction of limbic or reward pathways are considered as a potential cause. Indeed, apathy was found to be associated with impaired connectivity of limbic association tracts in patients with clinical SVD [55]. The results of the DTI studies of white matter connectivity and apathy in SSVD, however, were not conclusive [45 50].

## Cortical thinning, SSVD and apathy

The contradictory findings regarding the relationship between cortical thickness and apathy might be due to other mechanisms than SSVD leading to cortical thinning. Cortical thickness and WMH are associated, but they are not interchangeable [56 57]. Cortical thinning in the parietal lobes, anterior insula and caudate nuclei bilateral is related to WMH, but widespread cortical thinning is related to normal aging as well as early

Alzheimer's disease [56 57 58]. In the frontal regions, the temporal regions, and the anterior cingulate, all areas which have been studied specifically, cortical thinning could be caused by aging as well as Alzheimer's disease. Our review has shown that associations in the general population between apathy and the WMH-related regions of cortical thinning (parietal lobes, anterior insula and caudate nuclei) have not been studied yet. This is a consideration for future research, more than it is a counterargument for an association between SSVD and apathy.

### The vascular apathy hypothesis and the vascular depression hypothesis

Depression can be a confounder when looking for the relationship between vascular disease and apathy, since apathy may be a symptom of depression (anhedonia), while it has also been related to vascular disease [25 59].

Of the fourteen studies we reviewed, twelve controlled for depression [9 29 30 31 32 43 44 45 47 49 50 51]. In three of these latter studies the GDS was used as a measure of both apathy and depression [9 29 44] and in five articles [31 32 47 49 50] the GDS was used as a measure of depression, including the three apathy items of this scale. Since these GDS apathy items show a low sensitivity and a high specificity as a measure of apathy in older populations [38] correction for depression measured by the GDS may imply that apathy was also corrected for, attenuating the SSVD-apathy association. If depression was overcorrected for in these studies, the associations between SSVD and apathy may also have been stronger than the statistics now show.

On the other hand the role of apathy in the vascular depression hypothesis is often not accounted for in research while it may potentially act as a confounder. In patients with clinical SVD, apathy was associated with reduced white matter integrity, while depression was not, when apathy was controlled for [19 21]. Arguably, with the emerging evidence for the vascular apathy hypothesis one may wonder whether in research of the vascular depression hypothesis apathy was and is adequately corrected for.

## Limitations:

As stated, most of the research we reviewed was cross-sectional, preventing us from establishing whether SSVD precedes apathy, while we were also unable to determine whether more SSVD leads to higher levels of apathy. An alternative explanation for an apathy-SSVD or an SSVD-apathy relationship in cross-sectional designs is that apathy leads to poorer cardiovascular outcomes due to differences in health behaviours [14]. Does an association between CVRF and apathy then reflect the concept of vascular apathy our does it (partially) reflect differences in health behaviours that are caused by apathy? Nevertheless, the findings of an increase in the incidence of apathy with more cardiovascular pathologies [29] points towards CVRF as an aetiological factor in apathy (and not only the reverse mechanism).

Another methodological issue is the use of many different proxies for SSVD. The use of a broad array of SSVD proxies has negative consequences for the comparability of the research and precludes meta-analysis to estimate the magnitude of associations found. Nonetheless, generalizability increases when increasing levels of apathy are associated with widely different proxies for SSVD.

Finally, of the many different apathy scales that were employed, the AES and the NPI apathy subscale were the only tools that are well-validated [36 37], which is why we cannot rule out that the use of the other apathy scales may have negatively affected the quality of the results reported.

## Conclusion

The studies published to date show that WMH, cerebral microbleeds, cardiovascular disease, hypertension and ABI are associated with apathy in the general population. However, as most studies were cross-sectional in nature, the directions of the associations remain unclear and might be reciprocal/bidirectional. Finally, although the hypothesis of vascular apathy is supported by the available literature, more prospective evidence is needed.

*Table 2. Studies using Magnetic Resonance Imaging or Diffusion Tensor imaging*

| Author Year | Population<br>Study design<br>Number of participants | MRI†<br>DTI‡ | Proxy for subclinical small vessel disease | Apathy instrument | Results | Quality |
|---|---|---|---|---|---|---|
| Yao et al., 2009 | General population<br>Cross-sectional<br>222 | MRI† | Silent infarction<br>Deep WMH§ | Apathy scale | WMH§: odds ratio 1.826 (1.129-2.953) for apathy per grade WMH§; p=0.014 | High (10/16) |
| Cacciari et al., 2010 | MCI¶ patient<br>Cross-sectional<br>20 | DTI‡ | Mean diffusivity of white matter (20 pixels) | Italian dementia apathy interview and rating | Mean diffusivity of white matter is associated with apathy 4 areas | Not high (6/16) |
| Naka-mura et al, 2013 (55) | MCI¶ patients<br>Cross-sectional<br>516 | MRI† | vascularMCI¶ : ≥5 lacunar infarcts and white matter lesions | Clinical assessment of spontaneity | vascularMCI¶ was associated with apathy, more strongly than other MCI¶ | Not high (8/16) |
| Za-hodne et al, 2013 | MCI¶ patients<br>Longitudinal<br>334 | MRI† | Cortical thickness | Neuropsychiatric Inventory apathy scale | Entorhinal cortex: rate of change: 0.001 (0.001)<br>Orbitofrontal cortex: rate of change:-6e-4 (0.001)<br>Middle frontal gyrus: rate of change: 14.5e-4(0.001)<br>Anterior cingulate cortex: rate of change:-0.002 (0.001);<br>p<0.1; model corrected for depression: p=0.025 | High (7/9) |
| Grool et al, 2014 | General population<br>Cross-sectional<br>4354 | MRI† | WMH§ (total and region)<br>Total brain volume | GDS-3A†† | Total WMH§ volume: 1.07 (1.02-1.13); p=0.008 (model 2) | High (11/16) |
| Dono-van et al, 2014 | General population<br>Cross-sectional and (partly) longitudinal<br>812 | MRI† | Cortical thickness | Neuropsychiatric inventory apathy scale | Bilateral average cortical thickness and apathy over time; beta 0.35 (0.29-0.41); p<0.0001 | High (11/16) |

| Author Year | Population<br>Study design<br>Number of participants | MRI†<br>DTI‡ | Proxy for subclinical small vessel disease | Apathy instrument | Results | Quality |
|---|---|---|---|---|---|---|
| Guercio et al, 2015B | General population<br>Cross-sectional<br>66 | MRI† | Cortical thickness | Apathy evaluation scale | Inferior temporal cortex: beta 18.07 (6.45-29.70); p=0.004<br><br>Anterior cingulate cortex: beta-10.03 (-19.38—0.068); p=0.04 | Not high (7/16) |
| Delrieu et al, 2015 | MCI patients<br>Case-control<br>65 | MRI† and FDG-PET‡‡ | Brain volume<br>WMH§ volume<br>Reduced glucose metabolism | Neuropsychiatric inventory apathy scale | WMH§ and no apathy versus apathy 0.9 (0.5) versus 0.5 (0.1); p=0.678 | High (6/9) |
| Moonen et al, 2017 | General population<br>Cross-sectional<br>195 | MRI† and DTI‡ | Fractial anisotropy<br>Mean Diffusivity<br>Axial diffusivity<br>Radial diffusivity | Apathy scale | Fractial anisotropy: 0.62 (-0.04-1.028); p=0.07 (model 3) | High (10/16) |
| Xu et al., 2017 | General population<br>Cross-sectional<br>802 | MRI† | Cerebral microbleeds | Neuropsychiatric Inventory apathy scale | No cerebral microbleed versus one : 0.04 (0.39) versus 0.25 (1.44); p=0.02 | High (11/16) |

Legend: † MRI: magnetic resonance imaging; ‡ DTI: diffusion tensor imaging; § WMH: white matter hyperintensities; ¶ MCI: minimal cognitive impairment; †† GDS-3A: three apathy items of the geriatric depression scale; ‡‡ FDG-PET: fludeoglucose positron-emission tomography. High quality: ≥60% of the maximum score.

## References


1. Groeneweg-Koolhoven I, Ploeg M, Comijs HC, et al. Apathy in early and late-life depression. *J Affect Disord*. 2017;223:76-81. doi:10.1016/J.JAD.2017.07.022
2. Del-Monte J, Bayard S, Graziani P, Gély-Nargeot MC. Cognitive, Emotional, and Auto-Activation Dimensions of Apathy in Parkinson's Disease. *Front Behav Neurosci*. 2017;11. doi:10.3389/FNBEH.2017.00230
3. Robert P, Onyike CU, Leentjens AFG, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24(2):98-104. doi:10.1016/J.EURPSY.2008.09.001
4. Robert P, Lanctôt KL, Agüera-Ortiz L, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *Eur Psychiatry*. 2018;54:71-76. doi:10.1016/J.EURPSY.2018.07.008
5. Clarke D, Ko J, Lyketsos C, Rebok G, Eaton W. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr*. 2010;22(5):819-829.
6. Njomboro P, Deb S, Humphreys GW. Apathy symptoms modulate motivational decision making on the Iowa gambling task. *Behav Brain Funct*. 2012;8. doi:10.1186/1744-9081-8-63
7. Tierney SM, Woods SP, Weinborn M, Bucks RS. Real-world implications of apathy among older adults: Independent associations with activities of daily living and quality of life. *J Clin Exp Neuropsychol*. 2018;40(9):895-903. doi:10.1080/13803395.2018.1444736
8. Feast A, Orrell M, Charlesworth G, Melunsky N, Poland F, Moniz-Cook E. Behavioural and psychological symptoms in dementia and the challenges for family carers: systematic review. *Br J Psychiatry*. 2016;208(5):429-434. doi:10.1192/BJP.BP.114.153684
9. Ligthart S, Richard E, Fransen N, et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69(9):636-642.
10. Marijnissen RM, Bus BAA, Schoevers RA, et al. Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry*. 2014;22(8):801-810. doi:10.1016/j.jagp.2013.01.001
11. Moretti R, Signori R. Neural correlates for apathy: Frontal-prefrontal and parietal cortical- subcortical circuits. *Front Aging Neurosci*. 2016;8(DEC). doi:10.3389/fnagi.2016.00289
12. Eurelings LSM, van Dalen JW, ter Riet G, et al. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data. *Clin Epidemiol*. 2018;10:363-379. doi:10.2147/CLEP.S150915
13. Padala PR, Desouza C V., Almeida S, et al. The impact of apathy on glycemic control in diabetes: a cross-sectional study. *Diabetes Res Clin Pract*. 2008;79(1):37-41. doi:10.1016/J.DIABRES.2007.06.012

14. Eurelings LSM, Jaccard J, Moll Van Charante EP, et al. The mediating role of cardiovascular risk factors in the relationship between symptoms of apathy and incident cardiovascular disease in community-dwelling older individuals. *Int psychogeriatrics*. 2016;28(4):669-679. doi:10.1017/S1041610215001751

15. Yao H, Takashima Y, Araki Y, Uchino A, Yuzuriha T, Hashimoto M. Leisure-Time Physical Inactivity Associated with Vascular Depression or Apathy in Community-Dwelling Elderly Subjects: The Sefuri Study. *J Stroke Cerebrovasc Dis*. 2015;24(11):2625-2631. doi:10.1016/J.JSTROKECEREBROVASDIS.2015.07.018

16. Eurelings LSM, Ligthart SA, Van Dalen JW, Moll Van Charante EP, Van Gool WA, Richard E. Apathy is an independent risk factor for incident cardiovascular disease in the older individual: a population-based cohort study. *Int J Geriatr Psychiatry*. 2014;29(5):454-463. doi:10.1002/GPS.4026

17. Caeiro L, Ferro JM, Costa J. Apathy secondary to stroke: a systematic review and meta-analysis. *Cerebrovasc Dis*. 2013;35(1):23-39. doi:10.1159/000346076

18. Tu MC, Huang WH, Hsu YH, Lo CP, Deng JF, Huang CF. Comparison of neuropsychiatric symptoms and diffusion tensor imaging correlates among patients with subcortical ischemic vascular disease and Alzheimer's disease. *BMC Neurol*. 2017;17(1). doi:10.1186/S12883-017-0911-5

19. Hollocks MJ, Lawrence AJ, Brookes RL, et al. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain*. 2015;138(12):3803-3815. doi:10.1093/brain/awv304

20. Lohner V, Brookes RL, Hollocks MJ, Morris RG, Markus HS. Apathy, but not depression, is associated with executive dysfunction in cerebral small vessel disease. *PLoS One*. 2017;12(5). doi:10.1371/journal.pone.0176943

21. Tay J, Tuladhar AM, Hollocks MJ, et al. Apathy is associated with large-scale white matter network disruption in small vessel disease. *Neurology*. 2019;92(11):E1157-E1167. doi:10.1212/WNL.0000000000007095

22. Lavretsky H, Lesser IM, Wohl M, Miller BL, Mehringer CM. Clinical and neuroradiologic features associated with chronicity in late-life depression. *Am J Geriatr Psychiatry*. 1999;7(4):309-316. doi:10.1097/00019442-199911000-00006

23. Moonen JEF, De Craen AJM, Comijs HC, Naarding P, De Ruijter W, Van Der Mast RC. In depressed older persons higher blood pressure is associated with symptoms of apathy. The NESDO study. *Int psychogeriatrics*. 2015;27(9):1485-1493. doi:10.1017/S1041610215000253

24. Lampe IK, Heeren TJ. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *Int psychogeriatrics*. 2004;16(4):481-486. doi:10.1017/S1041610204000766

25. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. "Vascular depression" hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915-922. doi:10.1001/archpsyc.1997.01830220033006

26. Wouts L, Janzing JG, Lampe IK, et al. The interaction between cerebrovascular disease and neuroticism in late-life depression: A cross-sectional study. *Int J Geriatr Psychiatry*. 2011;26(7):702-710. doi:10.1002/gps.2584

27. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9(7):689-701. doi:10.1016/S1474-4422(10)70104-6

28. Rensma SP, van Sloten TT, Launer LJ, Stehouwer CDA. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2018;90:164-173. doi:10.1016/J.NEUBIOREV.2018.04.003

29. van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry*. 2008;23(3):266-271. doi:10.1002/GPS.1872

30. Yao H, Takashima Y, Mori T, et al. Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: the Sefuri brain MRI study. *Hypertens Res*. 2009;32(7):586-590. doi:10.1038/HR.2009.65

31. Donovan NJ, Wadsworth LP, Lorius N, et al. Regional cortical thinning predicts worsening apathy and hallucinations across the Alzheimer disease spectrum. *Am J Geriatr Psychiatry*. 2014;22(11):1168-1179. doi:10.1016/J.JAGP.2013.03.006

32. Guercio BJ, Donovan NJ, Ward A, et al. Apathy is associated with lower inferior temporal cortical thickness in mild cognitive impairment and normal elderly individuals. *J Neuropsychiatry Clin Neurosci*. 2015;27(1):e22-e27. doi:10.1176/APPI.NEUROPSYCH.13060141

33. Kuijpers T, Van Der Windt DAWM, Van Der Heijden GJMG, Bouter LM. Systematic review of prognostic cohort studies on shoulder disorders. *Pain*. 2004;109(3):420-431. doi:10.1016/J.PAIN.2004.02.017

34. Wells G, Shea B, O'Connell ME, et al. The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

35. Luppino FS, De Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220-229. doi:10.1001/ARCHGENPSYCHIATRY.2010.2

36. Weiser M, Garibaldi G. Quantifying motivational deficits and apathy: A review of the literature. *Eur Neuropsychopharmacol*. 2015;25(8):1060-1081. doi:10.1016/j.euroneuro.2014.08.018

37. Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, Marin RS. Are the available apathy measures reliable and valid? A review of the psychometric evidence. *J Psychosom Res*. 2011;70(1):73-97. doi:10.1016/J.JPSYCHORES.2010.01.012

38. Bertens AS, Moonen JEF, de Waal MWM, et al. Validity of the three apathy items of the Geriatric Depression Scale (GDS-3A) in measuring apathy in older persons. *Int J Geriatr Psychiatry*. 2017;32(4):421-428. doi:10.1002/GPS.4484

39. Guercio BJ, Donovan NJ, Munro CE, et al. The Apathy Evaluation Scale: A Comparison of Subject, Informant, and Clinician Report in Cognitively Normal Elderly and Mild Cognitive Impairment. *J Alzheimers Dis*. 2015;47(2):421-432. doi:10.3233/JAD-150146

40. Zeestraten EA, Benjamin P, Lambert C, et al. Application of Diffusion Tensor Imaging Parameters to Detect Change in Longitudinal Studies in Cerebral Small Vessel Disease. *PLoS One*. 2016;11(1). doi:10.1371/JOURNAL.PONE.0147836

41. Saji N, Kimura K, Yagita Y, Kawarai T, Shimizu H, Kita Y. Comparison of arteriosclerotic indicators in patients with ischemic stroke: ankle-brachial index, brachial-ankle pulse wave velocity and cardio-ankle vascular index. *Hypertens Res*. 2015;38(5):323-328. doi:10.1038/HR.2015.8

42. Laurent S, Boutouyrie P. The structural factor of hypertension: large and small artery alterations. *Circ Res*. 2015;116(6):1007-1021. doi:10.1161/CIRCRESAHA.116.303596

43. Sugawara N, Yasui-Furukori N, Umeda T, et al. Ankle brachial pressure index as a marker of apathy in a community-dwelling population. *Int J Geriatr Psychiatry*. 2011;26(4):409-414. doi:10.1002/GPS.2541

44. van Sloten TT, Mitchell GF, Sigurdsson S, et al. Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: cross-sectional findings from the AGES-Reykjavik Study. *J Psychiatry Neurosci*. 2016;41(3):162-168. doi:10.1503/JPN.140334

45. Cacciari C, Moraschi M, Di Paola M, et al. White matter microstructure and apathy level in amnestic mild cognitive impairment. *J Alzheimers Dis*. 2010;20(2):501-507. doi:10.3233/JAD-2010-1384

46. Nakamura K, Kasai M, Ouchi Y, et al. Apathy is more severe in vascular than amnestic mild cognitive impairment in a community: the Kurihara Project. *Psychiatry Clin Neurosci*. 2013;67(7):517-525. doi:10.1111/PCN.12098

47. Zahodne LB, Gongvatana A, Cohen RA, Ott BR, Tremont G. Are apathy and depression independently associated with longitudinal trajectories of cortical atrophy in mild cognitive impairment? *Am J Geriatr Psychiatry*. 2013;21(11):1098-1106. doi:10.1016/J.JAGP.2013.01.043

48. Grool AM, Geerlings MI, Sigurdsson S, et al. Structural MRI correlates of apathy symptoms in older persons without dementia: AGES-Reykjavik Study. *Neurology*. 2014;82(18):1628-1635. doi:10.1212/WNL.0000000000000378

49. Delrieu J, Desmidt T, Camus V, et al. Apathy as a feature of prodromal Alzheimer's disease: an FDG-PET ADNI study. *Int J Geriatr Psychiatry*. 2015;30(5):470-477. doi:10.1002/GPS.4161

50. Moonen JEF, Foster-Dingley JC, Van Den Berg-Huijsmans AA, et al. Influence of Small Vessel Disease and Microstructural Integrity on Neurocognitive Functioning in Older Individuals: The DANTE Study Leiden. *AJNR Am J Neuroradiol*. 2017;38(1):25-30. doi:10.3174/AJNR.A4934

51. Xu X, Chan QL, Hilal S, et al. Cerebral microbleeds and neuropsychiatric symptoms in an elderly Asian cohort. *J Neurol Neurosurg Psychiatry*. 2017;88(1):7-11. doi:10.1136/JNNP-2016-313271

52. Moroni F, Ammirati E, Rocca MA, Filippi M, Magnoni M, Camici PG. Cardiovascular disease and brain health: Focus on white matter hyperintensities. *Int J Cardiol Hear Vasc*. 2018;19:63-69. doi:10.1016/J.IJCHA.2018.04.006

53. Joutel A, Chabriat H. Pathogenesis of white matter changes in cerebral small vessel diseases: beyond vessel-intrinsic mechanisms. *Clin Sci (Lond)*. 2017;131(8):635-651. doi:10.1042/CS20160380

54. Aribisala BS, Morris Z, Eadie E, et al. Blood pressure, internal carotid artery flow parameters, and age-related white matter hyperintensities. *Hypertens (Dallas, Tex 1979)*. 2014;63(5):1011-1018. doi:10.1161/HYPERTENSIONAHA.113.02735

55. Lisiecka-Ford. DM, Tozer DJ, Morris RG, Lawrence AJ, Barrick TR, Markus HS. Involvement of the reward network is associated with apathy in cerebral small vessel disease. *J Affect Disord*. 2018;232:116-121. doi:10.1016/J.JAD.2018.02.006

56. Zhuang Y, Zeng X, Wang B, Huang M, Gong H, Zhou F. Cortical Surface Thickness in the Middle-Aged Brain with White Matter Hyperintense Lesions. *Front Aging Neurosci*. 2017;9(JUL). doi:10.3389/FNAGI.2017.00225

57. Lambert C, Sam Narean J, Benjamin P, Zeestraten E, Barrick TR, Markus HS. Characterising the grey matter correlates of leukoaraiosis in cerebral small vessel disease. *NeuroImage Clin*. 2015;9:194-205. doi:10.1016/J.NICL.2015.07.002

58. Silbert LC, Lahna D, Promjunyakul NO, et al. Risk Factors Associated with Cortical Thickness and White Matter Hyperintensities in Dementia Free Okinawan Elderly. *J Alzheimers Dis*. 2018;63(1):365-372. doi:10.3233/JAD-171153

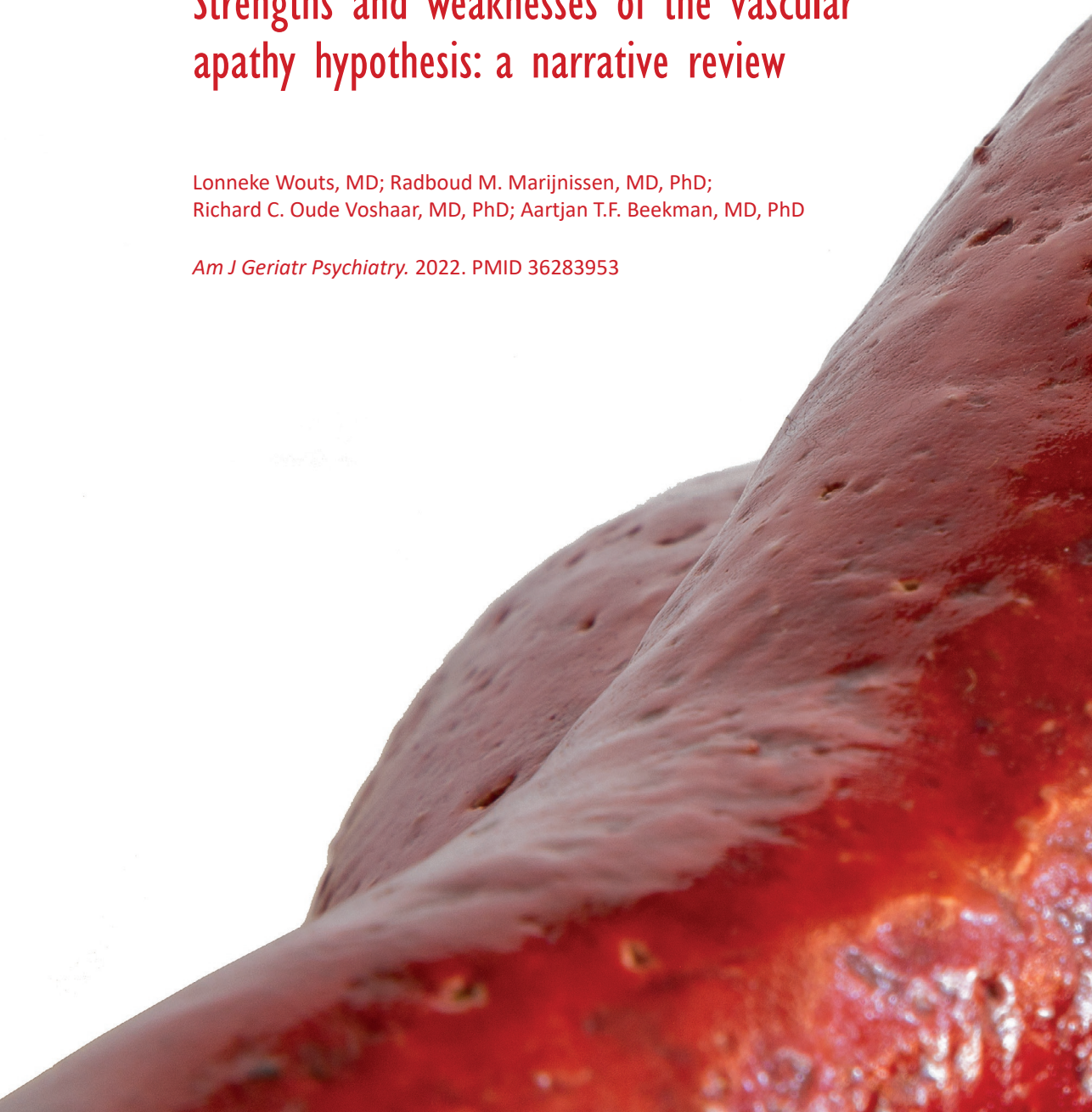
59. Baldwin RC, O'Brien J. Vascular basis of late-onset depressive disorder. *Br J Psychiatry*. 2002;180(FEB.):157-160. doi:10.1192/BJP.180.2.157

# Chapter 7

## Strengths and weaknesses of the vascular apathy hypothesis: a narrative review

Lonneke Wouts, MD; Radboud M. Marijnissen, MD, PhD;
Richard C. Oude Voshaar, MD, PhD; Aartjan T.F. Beekman, MD, PhD

*Am J Geriatr Psychiatry.* 2022. PMID 36283953



## Abstract

The vascular apathy hypothesis states that cerebral small vessel disease (CSVD) can cause apathy, even when no other symptoms of CSVD are present. In order to examine this hypothesis, the objectives of this narrative review are to evaluate the evidence for a pathophysiological mechanism linking CSVD to apathy and to examine whether CSVD can be a sole cause of apathy. The nature of the CSVD-apathy relationship was evaluated using the Bradford Hill criteria as a method for research on the distinction between association and causation. Pathological, neuroimaging, and behavioral studies show that CSVD can cause lesions in the reward network, which causes an apathy syndrome. Studies in healthy older individuals, stroke patients and cognitively impaired persons consistently show an association between CSVD markers and apathy, although studies in older persons suffering from depression are inconclusive. A biological gradient is confirmed, as well as a temporal relationship, although the evidence for the latter is still weak. The specificity of this causal relationship is low given there often are other contributing factors in CSVD patients with apathy, particularly depression and cognitive deterioration. Differentiating between vascular apathy and other apathy syndromes on the basis of clinical features is not yet possible, while in-depth knowledge about differences in the prognosis and efficacy of treatment options for apathy caused by CSVD and other apathy syndromes is lacking. Since we cannot differentiate between etiologically different apathy syndromes as yet, it is premature to use the term vascular apathy which would suggest a distinct clinical apathy syndrome.


## Introduction

As a clinical syndrome, apathy is characterized by diminished motivation, leading to a reduction in emotions, thoughts and initiative to perform activities [1]. Cerebral small vessel disease (CSVD), an atherosclerotic disease of the brain causing ischemic changes in the surrounding brain tissue, is suspected to be a cause of this frequent and disabling syndrome [2] [3]. Neuroimaging markers of CSVD include white matter hyperintensities (WMH), cerebral microbleeds, lacunar infarcts and visible perivascular spaces. Clinically, CVSD is associated with several symptoms and consequences, in particular cognitive impairment, problems with gait and balance and a higher incidence of depression, stroke, dementia, disability and death [4]. The vascular apathy hypothesis states that CSVD can be a sole cause of apathy, even in the absence of other symptoms of CSVD [5] [6] [7].

Apathy is seen in 2-6% of the general population, with its prevalence increasing with age [8]. Also the prevalence of CSVD increases with age, from 5% in people aged 50 years to almost 100% in those older than 90 years [9]. In CSVD populations 52% had severe apathy (based on the Apathy Scale and a median cut-off of 3) [10]. Given these high prevalence rates, the vascular apathy hypothesis is particularly relevant for older populations, even more so considering the often more profound consequences of apathy such as aggravated functional impairment [11], reduced quality of life [3], high caregiver burden [12] [13], and a raised risk of incident cardiovascular disease, stroke and mortality [14] and dementia [15].

Although attractive as a hypothesis, many questions remain unanswered. Questions that remain are whether CSVD is a true causal factor for apathy and whether it can be a sole cause of apathy. Furthermore, the term 'vascular apathy' suggests a distinguishable clinical syndrome, but is that claim truly supported by the evidence?

This information is not only relevant for researchers, but also for clinicians. Researchers need a clear overview on what we do and what we do not know to help devise relevant research designs to fill in the gaps in our knowledge. Clinicians need this information to decide on how to interpret symptoms of patients presenting with apathy and signs of CSVD on imaging and to decide on what information and advice to give to these patients and their relatives and/or caregivers.

### Objectives

The objective of the present narrative review article is twofold. We sought to gather and evaluate the evidence suggesting a pathophysiological mechanism linking CSVD and apathy and to examine whether the hypothesis that CSVD can be a sole cause of apathy has been substantiated.

## Methods

In order to be able to distinguish between association and causation, we tested the evidence using the Bradford Hill criteria [16 17], which are summarized in Table 1. No single criterion can prove causation, but each criterion adds to the credibility of causation.
In order to establish whether CSVD can cause apathy, we searched the literature for evidence on the *plausibility* and the *strength* of associations.

In addition, we assessed whether there is a *biological gradient*, we evaluated data on the *temporality* of associations and the *consistency* and *coherence* of the findings. Our second objective, to determine if CSVD can be a sole cause of apathy, was evaluated using the *specificity*-criterion.

We performed various searches to identify relevant research work (see supplementary material for each specific research question). ´White matter hyperintensities´, ´lacunar infarcts´, ´cerebral microbleeds´, ´cortical thickness´ and ´perivascular spaces´ were included in the search criteria for ´cerebral small vessel disease´. When we searched for a combination of cerebral small vessel disease and apathy, we also included ´vascular apathy´ as a search term. Searches were performed in PUBMED, English language, on December the 9th, 2021. Abstracts of all articles were checked for relevance by the first author (LW). For some of the research questions recent (structured) reviews and meta-analyses were available. Information on other more recent research work which was not included in these (structured) reviews or meta-analyses was added when relevant to the argumentation.

*Table 1. Bradford-Hill criteria for causation*

| Criterion | Description |
|---|---|
| *Plausibility* | There is a rational, logical basis for an association. |
| *Strength* | The association is strong. |
| *Temporality* | The cause precedes the effect. |
| *Biological gradient* | There is a dose-response relationship. |
| *Consistency* | The association is established in multiple observations in different populations under different circumstances. |
| *Specificity* | The outcome is best predicted by one primary factor. |
| *Coherence* | The association is coherent with other knowledge. |
| *Experimental evidence* | The association is confirmed in experimental designs. |
| *Analogy* | An analogue phenomenon in another area is already accepted. |

For the *plausibility*-criterion we looked into the pathophysiological mechanisms that would link CSVD to apathy, thus supporting a causal relationship. To establish the *strength* of the association we looked into the odds ratios (OR), standard mean differences (SMD) and (clinical) significance of associations between CSVD biomarkers and apathy measures. A *biological gradient* was established if the level of CSVD was associated with the level of apathy. The *temporality*-criterion was fulfilled if the CSVD-apathy association was established in prospective studies. The *consistency* was based on the diversity of populations and circumstances in which the association was established and on the validity of the methods used to asses CSVD and apathy. Moreover, we established if these findings were *coherent* with results from other areas of research.

In our context *specificity* is established when the outcome (apathy) is best predicted by this one primary factor (CSVD). Hence, we looked at other important risk-factors for apathy and to what extent these could have influenced the results of studies assessing the CSVD-apathy association.

The criterion of *experimental evidence* cannot be evaluated since no cure for CSVD is yet established. Bradford-Hill stated that the criterion of *analogy* can provide some circumstantial additional support [16], but it is not a core criterion for causation and we chose not to use it as evidence in this narrative review.

# Results

## Plausibility

What pathophysiological mechanisms would link CSVD to apathy? In CSVD the small perforating arterioles, the capillaries and probably the venules of the brain are dysfunctioning, causing lesions. WMH, cerebral microbleeds, lacunar infarcts and perivascular spaces are biomarkers of CSVD, visible on neuroimaging [18]. It concerns a

whole-brain disease and the lesions it causes are probably more dynamic than earlier thought: regions without visible lesions on neuroimaging can actually dysfunction, while regions with visible lesions sometimes regenerate [4]. In general though, it is a progressive disease [4 18]. Also, although upon pathological examination of the brains of CSVD patients not all radiological lesions seem to represent actual lesions, most do [19]. Furthermore, an increasing total CSVD burden or progression of WMH load does seem to reflect progression in CSVD severity [20 18]. It is therefore plausible that radiologically observed CSVD manifests as pathological lesions in the brain and that these lesions can hinder brain circuitries.

Imaging studies across patient populations (including populations of patients with neurodegenerative diseases, acquired brain injury, psychiatric disorders or Parkinson´s disease) have related apathy to white matter lesions in the frontal, striatal and anterior cingulate pathways, to basal ganglia lesions and to lesions in the parietal pathways [21 22 23]. Pathway analyses revealed that network disruption mediated the relationship between CSVD markers and apathy [24]. But how do lesions in these pathways lead to apathy?

Diffusion tensor imaging and functional imaging studies in humans have shown that effort-based decision making tasks are related to the frontal and striatal regions, including the medial orbitofrontal cortex, the anterior cingulate cortex (ACC) and the basal ganglia including the ventral striatum [25]. Connectivity in these pathways, which together are called the reward network, was reduced in CSVD patients with apathy (and connectivity was not reduced in motor or visual networks) [26]. The link between this reward network and apathy would then be as follows: when, at the functional level, the process of effort-based decision making is disturbed, we see an apathy syndrome at the clinical level. And indeed, when behavioral paradigms were applied in CSVD patients, those with apathetic symptoms were less responsive to rewards and less inclined to investing efforts [27 28].

The plausibility of a pathophysiological link between CSVD and apathy has thus been convincingly demonstrated.



## Strength and biological gradient

What information do we have on the strength of a CSVD-apathy relationship and does the severity of CSVD predict the level of apathy?

In a recent meta-analysis of apathy studies including healthy individuals, persons with cognitive deficits and/or stroke, larger WMH volumes were significantly associated with apathy, with an OR of 1.41 (95% CI 1.05-1.89) and a standard mean difference (SMD) in apathy scores on the Apathy Evaluation Scale (AES)[29] between WMH severities (low or high) of 0.38 (95% CI 0.15-0.61) [30]. In a large diffusion tensor imaging (DTI) study CSVD patients were significantly more apathetic than healthy controls, with the microstructural white matter changes in the CSVD sample showing a strong relationship with apathy [10]. In older adults receiving treatment for depression evidence of an WMH-apathy association was less consistent than in the populations referred to earlier (healthy older adults and

older adults with cognitive impairment and/or stroke). One study did find an association [31], one did not [32], and in a severely depressed population the WMH-apathy association was established in participants with late-onset depression only [33].

Other CSVD biomarkers than WMH could not be systematically analyzed, due to the large heterogeneity with respect to CSVD biomarkers, apathy scales and research designs across studies. In those investigating the association between lacunes and apathy, some reported confirmatory [34 35] and some negative results [26 36].

As to subcortical infarcts, most studies supported a clinically significant association with apathy, but because of the heterogeneity in their designs the strength of the association remains unclear. Finally, no evidence was found to suggest that microbleeds or perivascular spaces are associated with apathy [37 38 26 36].

While most research uses WMH as a biomarker of CSVD, this might not be the best index since CSVD causes widespread disruptions in cerebral connections. Given that CSVD concerns a whole- brain disease, studies focusing on a particular type of MRI finding (for instance only WMH) might thus miss the larger picture, where the use of a composite score -which combines information on CSVD neuroimaging biomarkers- might be more informative [20 4]. A high total CSVD burden raised the odds of having apathy in post-stroke patients (OR 3.61; 95% CI 1.34-9.68) [39] and in a CSVD sample apathy was associated with the total CSVD burden ($R^2$=0.332; t=4.134; p<0.00) [40].

Numerous studies only examined whether CSVD markers such as WMH predicted apathy, without looking for evidence of a dose-response effect [26 41 42 37 36 43 44 45 46 47 48 49 10 31 32]. The studies that did do so are summarized here to evaluate the support for a biological gradient. In healthy older adults the WMH grade was found to correlate with apathy [50]. In geriatric outpatients WMH volume was related to apathy [51]. In a study of Alzheimer's disease patients WMH volume was not related to apathy as measured by NPI score [52], while in a small study in patients with probable Alzheimer's disease frontal WMH volume was related to apathy [53]. In patients diagnosed with subcortical vascular cognitive impairment each additional lacuna and higher WMH volumes were both related to the severity of apathy [35], while in another cohort of subcortical vascular patients with mixed cognitive status higher lacunar volume in WMH was related to the presence of apathy [34].

In stroke patients the periventricular white matter hyperintensity score and the number of pontine infarcts were associated with apathy [54], while a gradient between total CSVD burden and risk of apathy was established in another cohort of stroke patients [39]. Finally, the extent of the total CSVD burden predicted apathy in CSVD patients [40].

In two cohort-studies of SVD patients white matter connectivity measures were significantly associated with apathy, while WMH volume or the number of lacunar infarcts (when depression and cognition were corrected for) were not, suggesting it might be *large-scale* white matter network disruption specifically which is associated with apathy [24 26].

Although, all in all, we can safely conclude that there is a dose-response relationship between CSVD and apathy in a diversity of populations, these results could do with replication. And particularly the association between the total CSVD burden and the severity of apathy needs further looking into, since this might be a more accurate biomarker for underlying network disruption.

## Temporality

Prospective studies supporting an association between CSVD at baseline and apathy at follow-up, or between CSVD progression and changes in apathy scores over time, add credibility to a causal relationship. Neuroimaging studies assessing frontal subcortical atrophy or WMH within 24 hours of a stroke found an association with apathy at 3 to 6 months of follow-up [55] [37] [56], barring a small scale study [36]. A study in which neuroimaging was conducted 3 months post-stroke and apathy assessed the next year also found no evidence of an association [39]. A study comparing baseline WMH volumes and apathy severity scores after 5 years in otherwise healthy individuals also found no evidence linking baseline WMH values to changes in apathy [57]. A study aiming to compare the differences in the course of neuropsychiatric symptoms between patients with Alzheimer´s disease and vascular dementia patients with WMH and lacunar infarcts on neuroimaging, found a higher level of apathy and a significant increase in apathy in the latter group, which was not related to cognitive decline [58]. The baseline WMH volumes of depressed patients receiving electric convulsive treatment (ECT) did not predict apathy post ECT but remaining depressive symptomatology and apathy at baseline did [32].

All in all, the temporal relationship between CSVD and apathy has some empirical support but this is thus far limited to stroke patients. Of note is that all these studies looked at the association between baseline WMH and apathy at follow-up. Studies investigating the progression of CSVD or WMH over time and its relation to changes in apathy were still lacking.

## Consistency

Are the reported associations between (markers of) CSVD and apathy consistent across a diversity of populations and contexts? Mostly, the evidence was obtained in healthy (older) adults and individuals with cognitive deficits and/or stroke [7] [30]. The few studies that specifically studied the WMH-apathy association in individuals with Parkinson's disease showed that apathy was predicted by WMH integrity [59] and that apathy severity was associated with WMH severity [60]. In depression, or after depression, findings are inconsistent. No association was found in older adults stills showing apathy following ECT for depression [32], but in depressed age peers who showed remaining symptoms of apathy after treatment with citalopram an association was found with white matter (and anterior cingulate) volumes [31], while WMH correlated with apathy in older adults with severe late-onset depression [33], but not in those with severe early-onset depression. Possible explanations for these inconsistencies will be discussed in the *Specificity* section.

The age range and demographic characteristics of study populations were diverse. The majority of studies looked at adults and often at older adults, including community-dwelling individuals and/or (mildly or severely) functionally impaired inpatients or outpatients. Study participants resided in European, North-American and Asian countries, no data were available on residents of South- and Central-America, Africa and Australia. Overall, the WMH-apathy association was consistent across the study populations. Associations between other neuroimaging markers or the total CSVD burden and apathy have received less broad attention as yet.

We next looked at measurement instruments for either CSVD or apathy and whether associations were consistent regardless of the techniques applied. CSVD was mainly investigated using magnetic resonance imaging, diffusion tensor imaging or positron emission tomography scans, with which WMH, lacunes (number or volumes), subcortical infarcts, microbleeds, perivascular spaces or total CSVD burden were assessed [20]. Studies measuring WMH [30], WMH network connectivity [24 26] and total CSVD burden consistently showed associations with apathy [39 40]. Studies focusing on other neuroimaging markers of CSVD were scarce or showed inconsistent results.

The studies involved used a diversity of apathy scales, but most widely used and validated, i.e., the AES [8 24 37 39 54 31], the apathy scale (AS) [61 55 53 47 50 32 33], the apathy scale of the Neuropsychiatric Inventory [62 42 52 35 44 45 58 48 49 40] and the 3A scale of the Geriatric Depression Scale (GDS 3A)[63 64 26 46 10]. We could not establish a pattern demonstrating that one scale yielded different results regarding the CSVD-apathy association than other scales. It is known, however, that in cognitively impaired persons self-reported apathy is not as reliable as clinician of informant rated indices [8]. Since evidence of a CSVD-apathy association was obtained in different populations, and not exclusively in individuals with cognitive impairment, and since many of these latter studies used clinician or informant rated scales, it is not likely that this (significantly) influenced the results.

## Coherence

Is the causal relationship between CSVD and apathy coherent with knowledge from other sources of information?

In rats, damage to the mediofrontal pathways disturbs effort-based decision making: rather than seeking large rewards at the expense of great effort, they were more likely to choose smaller rewards demanding less effort [65].

In humans, apathy is a common symptom following bilateral anterior cingulotomy, a procedure for therapy resistant severe chronic pain in which the ACC is cleaved [66], and also frequently mentioned in case-reports of brain damage of the ACC [67]. Apathy was also noted in a study of 114 patients with iatrogenic brain damage due to radiotherapy of the whole brain for primitive cerebral neoplasia, where the level of apathy depended on the cumulative doses of radiotherapy and was associated with the extent of the white matter damage [68].

Hence, we conclude a causal relationship between CSVD and apathy is coherent with knowledge from other areas of research.

## Specificity

To evaluate the specificity of the CSVD-apathy association we will look at other relevant risk-factors for apathy and if these could have confounded the results.

Particularly in older populations, physical and motor disabilities, a diminished level of consciousness (as seen in delirium), substance use (for instance use of antipsychotics or benzodiazepines) or major changes in the patients environment are well-established and highly relevant risk-factors for apathetic behavior [69 70 71 72 73]. These are ruled out in the diagnostic criteria for apathy [1], but most epidemiological research, especially in the general population, uses apathy rating scales rather than a broader clinical assessment [7]. Of the 27 studies on the CSVD-apathy association which we assessed for this narrative review only 9 controlled for the use of sedatives[34 35 44 45 48 49 31 32 40], the other studies did not or to a limited extent (i.e. only antidepressants), and only 8 controlled for physical impairment [37 36 35 40 47 58 56 49].

In the brain, motivation, initiative and execution, -which are diminished in the apathy syndrome-, involve generating and weighing options, reaching a decision, generating arousal and acting, where the ability to anticipate, desire and like the outcome acts as a reward system and self-stimulating feedback loop [74]. Besides the various brain areas forming the reward network [75] also multiple neurotransmitter systems that can be affected by neurodegeneration, such as the dopamine and serotonin systems, play a role in these processes [74 22]. And not only the reward network, but also the salience network,-a network that processes emotional information and activates other networks to respond-, is associated with apathy and particularly in depression this network might be functionally affected [76 23 77].

Depressive disorder is a frequent and relevant risk-factor for apathy, with apathy in late-life depression posing a risk for treatment resistance and often persevering, particularly in those with residual depressive symptoms [32 72].

Except for a few studies of the CSVD-apathy relationship which only partially corrected for the presence of a depressive disorder [52 26], all studies considered in this narrative review acknowledged, assessed and corrected for this possible confounder.
There is yet another highly relevant pathway causing apathy in late-life: cognitive impairment [72 69]. Apathy in late-life, particularly in those with depression as well, is associated with cognitive impairment and dementia [78 15 79]. In all studies on the CSVD-apathy relationship evaluated here, cognitive impairment was assessed and corrected for, although in some studies only to a limited extent (i.e. exclusion of participants with severe cognitive dysfunction) [26 39].

Furthermore, not only CSVD but also large vessel ischemic or hemorrhagic stroke has been shown to be associated with apathy [38]. Could large vessel stroke act as a confounder the studies under review? This is not very likely, since only 2 studies did not report on the presence of stroke [24 42], 4 studies included stroke patients only [41 37 39 36], while all the other studies excluded participants with a history of stroke [45 51 46 31 32 33 40] or with signs of large vessel stroke on neuroimaging [26 52 43 34 50 35 44 47 54 53 58 48 49 10].

In conclusion, the majority of the studies on the CSVD-apathy association might be confounded by the use of (sedative) medication or physical impairment, which is a weakness in the body of evidence supporting this relationship.

While the presence of depressive disorder, cognitive impairment and stroke are well controlled for in most studies, particularly in old-age these risk-factors often co-occur with CSVD and might still contribute in causing an apathy syndrome in the individual. And indeed, in individuals with apathetic behavior showing CSVD on neuroimaging there was not seldom an interplay between cognitive impairment, depressive disorder and apathy [72 79 48]. Hence, the specificity of the causal relationship between CSVD and apathy is low.

# Discussion

## CSVD and apathy: a causal relationship?

In conclusion, there is evidence that not only shows an association between WMH as a biomarker of CSVD and apathy but also supports a causal relationship between CSVD and apathy. Nevertheless, the evidence of a temporal and dose-response relationship is still weak and would benefit from prospective studies investigating the relationship between total CSVD burden (or WMH) change and change in apathy severity, most preferably in or comparing different, well-characterized populations.

Better still would be if imaging techniques were applied, -such as DTI-, that provide information on the disruption of networks, in prospective studies on apathy and apathy severity, since not only the volume of WMH or total CSVD burden, but also the *location of the damage* due to WMH or CSVD might be a determining factor in the extent of network destruction in the brain.

## Vascular apathy: a distinct clinical syndrome?

Although there is evidence to support that CSVD can be a cause and possibly a sole cause of an apathy syndrome, this does not mean that use of the term ´vascular apathy´ as a subcategory of the more generic term ´apathy syndrome´ is applicable to clinical practice. One of the objectives of this narrative review was to establish if we can say that vascular apathy is a clinical syndrome in its own right, i.e., a combination of symptoms resulting from a single cause or so commonly occurring together as to constitute a distinct clinical picture?

First, can we make unequivocal distinctions between vascular apathy and other clinical presentations of CSVD? It is not too difficult to discriminate between vascular apathy and Binswanger's disease [80], vascular parkinsonism [81] and subcortical vascular dementia [82], since patients with these conditions present with other distinctive symptoms (gait disturbances in vascular parkinsonism), more symptoms (not only apathy, but also gait disturbances, MCI and bladder dysfunction in Binswanger's disease), or more and more severe symptoms (severe cognitive impairment affecting overall daily functioning in subcortical vascular dementia). However, subcortical MCI and the depressive-executive subtype of depression are more difficult to discriminate from vascular apathy. Neuropsychological testing will help to establish subcortical MCI, as in MCI one of the cognitive domains is affected, -in *subcortical* MCI often semantic memory, executive/attentional functioning, visuospatial functioning or perceptual skills [82]- without problems in daily functioning.

When only apathetic symptoms are present the criteria for a depressive disorder are not met (DSM-5; 2013). Still, discriminating between apathy as part of a depressive disorder, or apathy as an independent syndrome remains difficult in individuals coping with a depressive disorder, since anhedonia, loss of interest, indecisiveness and psychomotor retardation are symptoms that characterize both disorders [83] (see Table 2). Interestingly, in a CSVD study investigating the process of effort-based decision making, a high resistance to efforts and a low response to rewards was seen in the patients with apathy, while the depressed CSVD patients showed a different decision-making pattern, with a higher decision making boundary, reflecting a need for more information before making a decision [28]. In the future behavioral tests might help to discriminate between apathetic and depressed CSVD patients, but to date these new behavioral paradigms have only been applied in apathy studies [25].

*Table 2. Overlapping and distinguishing symptoms between apathy and depression*

| **Apathy diagnostic criteria (2018)** | **Depression diagnostic criteria (DSM-5)** |
|---|---|
| (A) A quantitative reduction of goal-directed activity (behavioural, cognitive, emotional or social) in comparison to the patient's previous level of functioning. (B) Symptoms of at least 2 of the 3 following dimensions for at least 4 weeks. (C)These symptoms cause clinically significant impairment in functioning. (D) The symptoms are not solely attributable to physical or motor disabilities, a diminished level of consciousness, substance use or major changes in the patient's environment. | (A)The individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure (core criteria). (B) Collectively, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. (C)These symptoms must not be caused by a somatic condition or use of medication or drugs. (D)These symptoms must not be caused by another psychiatric disorder. (E) No manic or hypomanic episodes |
| ***Overlapping symptoms*** | |
| B1 BEHAVIOUR AND COGNITION: reduced general level of activity; diminished persistence of activity; less interest or slow in making choices; less interest in external issues; less interest in own health and image. | 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.<br>5. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).<br>8. Diminished ability to think or concentrate, or indecisiveness, nearly every day. |
| B2 EMOTION: less spontaneous emotion; fewer emotional reactions to the environment; less concern about the impact of actions/feelings on others; less empathy; less use of verbal or physical expressions | 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. |
| B3 SOCIAL INTERACTION: less spontaneous social initiative; less environmentally stimulated social interaction; decreased interest in interactions with family members; less verbal interaction; being more homebound | 5. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down). |
| ***Distinguishing symptoms*** | |
| | 1. Depressed mood most of the day, nearly every day.<br>3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.<br>4. Insomnia or hypersomnia nearly every day.<br>6. Fatigue or loss of energy nearly every day.<br>7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.<br>9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. |

Moreover, to our knowledge no studies have been performed that compared clinical symptoms of apathy in CSVD patients to clinical symptoms of apathy in other populations. And, given that currently there is no convincing evidence to suggest that vascular apathy is *clinically* distinct from apathy due to other causes both are diagnosed according to the same consensus criteria [1].

Moreover, when CSVD is identified as the likely cause of apathy, this does not alter the treatment since no specific other options have been developed. Monitoring both systolic and diastolic blood pressure should be emphasized [84], while physical activity, occupational therapy and/or cognitive interventions are the non-pharmacological treatments of choice [85]. The evidence for the efficacy of pharmacological interventions is still weak and confined to specific populations, and for CSVD related-apathy no such evidence exists [86 87].

Further, often CSVD will not be the sole cause of apathy. According to the diagnostic criteria [1] sedative medication, physical impairment and important psychosocial changes that induce apathetic behavior should be ruled out before diagnosing an apathy syndrome, but even then, other causes of apathy, -in particular neurodegenerative processes and depression-, often co-occur with CSVD [72 79 48] .

In conclusion, based on our review of the literature we can argue that the use of the term vascular apathy is justified by the evidence that CSVD is a cause of apathy. Furthermore, apathy in CSVD patients can often be distinguished from other clinical syndromes which are associated with CSVD.

However, there are no data to support that vascular apathy is different from other apathy syndromes in clinical presentation or treatment options and it accordingly does not qualify as a distinct clinical syndrome. The term *vascular apathy* would at this moment merely refer to the probable cause of the apathy and not to a clinically different syndrome. Further, since CSVD may often not be the sole cause of apathy and in clinical practice one cannot always be certain about which of several contributing factors is the most important, we recommend using the non-specific term *apathy syndrome* for the time being.



## Limitations

The Bradford-Hill criteria which were used to evaluate the causal relationship between CSVD and apathy were not intended as a “check-list” of criteria, but as criteria to consider when distinguishing between association or causation [16]. We aimed to stay true to this way of thinking. In our opinion, a narrative review better suited this purpose than a structured review or meta-analysis would, since in a narrative review a broader scope of evidence and arguments can be presented and more emphasis is put on the process of weighing of evidence and arguments.

The main limitation of this choice-the other side of the coin- is that in narrative review literature searches are not performed twice, the included studies are not as thoroughly weighed on quality by two authors as they would be in a structured review and data are not pooled as in a meta-analysis.

Furthermore, we limited the sources of information to published articles, it would have been interesting to gather expert opinions, for instance by means of the Delphi method.

Another limitation comes with applying the Bradford-Hill criteria to the CSVD-apathy association: there are no experimental data, only observational data [88] to support a causality claim.

## Conclusion

Consistent pathophysiological evidence linking CSVD and apathy makes it plausible that CSVD can cause apathy. This causal relationship is supported by the evidence on the strength and biological gradient of the CSVD-apathy associations obtained in a diversity of populations, although the evidence for a temporal relationship is still weak. Given that there are often other factors in patients with CSVD that may cause or contribute to apathy, the specificity of the causal relationship can be said to be low. It is premature to speak of vascular apathy as if referring to a distinct clinical apathy syndrome, since differentiation between apathy syndromes on the basis of clinical features is unfeasible, while in-depth knowledge about differences in the prognosis and efficacy of dedicated treatment for apathy caused by CSVD and other apathy syndromes is lacking.

## References


1. Robert P, Lanctôt KL, Agüera-Ortiz L, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *Eur Psychiatry*. 2018;54:71-76. doi:10.1016/J.EURPSY.2018.07.008
2. Tierney SM, Woods SP, Weinborn M, Bucks RS. Real-world implications of apathy among older adults: Independent associations with activities of daily living and quality of life. *J Clin Exp Neuropsychol*. 2018;40(9):895-903. doi:10.1080/13803395.2018.1444736
3. Groeneweg-Koolhoven I, de Waal M, van der Weele, GM Gussekloo J, van der Mast R. Quality of life in community-dwelling older persons with apathy. *Am J Geriatr Psychiatry*. 2014;22(2):186-194.
4. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. *Stroke Vasc Neurol*. 2016;1(3):83-92. doi:10.1136/SVN-2016-000035
5. Ligthart SA, Richard E, Fransen NL, et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69(6):636-642. doi:10.1001/archgenpsychiatry.2011.1858
6. Marijnissen RM, Bus BAA, Schoevers RA, et al. Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry*. 2014;22(8):801-810. doi:10.1016/j.jagp.2013.01.001
7. Wouts L, Kessel M van, Beekman ATF, Marijnissen RM, Voshaar RCO. Empirical support for the vascular apathy hypothesis: A structured review. *Int J Geriatr Psychiatry*. 2020;35(1):3-11. doi:10.1002/GPS.5217
8. Guercio BJ, Donovan NJ, Munro CE, et al. The Apathy Evaluation Scale: A Comparison of Subject, Informant, and Clinician Report in Cognitively Normal Elderly and Mild Cognitive Impairment. *J Alzheimers Dis*. 2015;47(2):421-432. doi:10.3233/JAD-150146
9. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: A clinical review. *Neurology*. 2019;92(24):1146-1156. doi:10.1212/WNL.0000000000007654
10. Hollocks MJ, Lawrence AJ, Brookes RL, et al. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain*. 2015;138(12):3803-3815. doi:10.1093/brain/awv304
11. Burton RL, O'Connell ME, Morgan DG. Cognitive and Neuropsychiatric Correlates of Functional Impairment Across the Continuum of No Cognitive Impairment to Dementia. *Arch Clin Neuropsychol*. 2018;33(7):795-807. doi:10.1093/ARCLIN/ACX112
12. Tsai CF, Hwang WS, Lee JJ, et al. Predictors of caregiver burden in aged caregivers of demented older patients. *BMC Geriatr*. 2021;21(1). doi:10.1186/S12877-021-02007-1
13. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al. Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. *Parkinsonism Relat Disord*. 2015;21(6):629-634. doi:10.1016/J.PARKRELDIS.2015.03.024

14. Eurelings LSM, van Dalen JW, ter Riet G, et al. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data. *Clin Epidemiol*. 2018;10:363-379. doi:10.2147/CLEP.S150915

15. Van Dalen JW, Van Wanrooij LL, Moll Van Charante EP, Brayne C, Van Gool WA, Richard E. Association of Apathy With Risk of Incident Dementia: A Systematic Review and Meta-analysis. *JAMA psychiatry*. 2018;75(10):1012-1021. doi:10.1001/JAMAPSYCHIATRY.2018.1877

16. Hill AB. The environment and disease: association or causation? *J R Soc Med*. 2015;108(1):32-37. doi:10.1177/0141076814562718

17. Feldman R, Meiman J, Stanton M, Gummin DD. Culprit or correlate? An application of the Bradford Hill criteria to Vitamin E acetate. *Arch Toxicol*. 2020;94(6):2249-2254. doi:10.1007/S00204-020-02770-X

18. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684-696. doi:10.1016/S1474-4422(19)30079-1

19. Humphreys CA, Smith C, Wardlaw JM. Correlations in post-mortem imaging-histopathology studies of sporadic human cerebral small vessel disease: A systematic review. *Neuropathol Appl Neurobiol*. 2021;47(7):910-930. doi:10.1111/NAN.12737

20. Staals J, Makin SDJ, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83(14):1228-1234. doi:10.1212/WNL.0000000000000837

21. Kos C, van Tol MJ, Marsman JBC, Knegtering H, Aleman A. Neural correlates of apathy in patients with neurodegenerative disorders, acquired brain injury, and psychiatric disorders. *Neurosci Biobehav Rev*. 2016;69:381-401. doi:10.1016/J.NEUBIOREV.2016.08.012

22. Thobois S, Prange S, Sgambato-Faure V, Tremblay L, Broussolle E. Imaging the Etiology of Apathy, Anxiety, and Depression in Parkinson's Disease: Implication for Treatment. *Curr Neurol Neurosci Rep*. 2017;17(10). doi:10.1007/s11910-017-0788-0

23. Pimontel MA, Kanellopoulos D, Gunning FM. Neuroanatomical Abnormalities in Older Depressed Adults With Apathy: A Systematic Review. *J Geriatr Psychiatry Neurol*. 2020;33(5):289-303. doi:10.1177/0891988719882100

24. Tay J, Tuladhar AM, Hollocks MJ, et al. Apathy is associated with large-scale white matter network disruption in small vessel disease. *Neurology*. 2019;92(11):E1157-E1167. doi:10.1212/WNL.0000000000007095

25. Pessiglione M, Vinckier F, Bouret S, Daunizeau J, Le Bouc R. Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. *Brain*. 2018;141(3):629-650. doi:10.1093/BRAIN/AWX278

26. Lisiecka-Ford. DM, Tozer DJ, Morris RG, Lawrence AJ, Barrick TR, Markus HS. Involvement of the reward network is associated with apathy in cerebral small vessel disease. *J Affect Disord*. 2018;232:116-121. doi:10.1016/J.JAD.2018.02.006

27. Le Heron C, Manohar S, Plant O, et al. Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease. *Brain*. 2018;141(11):3193-3210. doi:10.1093/brain/awy257

28. Saleh Y, Le Heron C, Petitet P, et al. Apathy in small vessel cerebrovascular disease is associated with deficits in effort-based decision making. *Brain*. 2021;144(4):1247-1262. doi:10.1093/BRAIN/AWAB013

29. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. *Psychiatry Res*. 1991;38(2):143-162. doi:10.1016/0165-1781(91)90040-V

30. Clancy U, Gilmartin D, Jochems ACC, Knox L, Doubal FN, Wardlaw JM. Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis. *The lancet Psychiatry*. 2021;8(3):225-236. doi:10.1016/S2215-0366(20)30431-4

31. Yuen GS, Gunning FM, Woods E, Klimstra SA, Hoptman MJ, Alexopoulos GS. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *J Affect Disord*. 2014;166:179-186. doi:10.1016/j.jad.2014.05.008

32. Carlier A, van Exel E, Dols A, et al. The course of apathy in late-life depression treated with electroconvulsive therapy; a prospective cohort study. *Int J Geriatr Psychiatry*. 2018;33(9):1253-1259. doi:10.1002/gps.4917

33. Oudega ML, Siddiqui A, Wattjes MP, et al. Are Apathy and Depressive Symptoms Related to Vascular White Matter Hyperintensities in Severe Late Life Depression? *J Geriatr Psychiatry Neurol*. 2021;34(1):21-28. doi:10.1177/0891988720901783

34. Lavretsky H, Zheng L, Weiner MW, et al. The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. *Int J Geriatr Psychiatry*. 2008;23(10):1040-1050. doi:10.1002/gps.2030

35. Kim HJ, Kang SJ, Kim C, et al. The effects of small vessel disease and amyloid burden on neuropsychiatric symptoms: a study among patients with subcortical vascular cognitive impairments. *Neurobiol Aging*. 2013;34(7):1913-1920. doi:10.1016/J.NEUROBIOLAGING.2013.01.002

36. Cosin C, Sibon I, Poli M, et al. Circadian sleep/wake rhythm abnormalities as a risk factor of a poststroke apathy. *Int J Stroke*. 2015;10(5):710-715. doi:10.1111/IJS.12433

37. Carnes-Vendrell A, Deus J, Molina-Seguin J, Pifarré J, Purroy F. Depression and Apathy After Transient Ischemic Attack or Minor Stroke: Prevalence, Evolution and Predictors. *Sci Rep*. 2019;9(1). doi:10.1038/S41598-019-52721-5

38. Douven E, Köhler S, Rodriguez MMF, Staals J, Verhey FRJ, Aalten P. Imaging Markers of Post-Stroke Depression and Apathy: a Systematic Review and Meta-Analysis. *Neuropsychol Rev*. 2017;27(3):202-219. doi:10.1007/S11065-017-9356-2

39. Douven E, Staals J, Freeze WM, et al. Imaging markers associated with the development of post-stroke depression and apathy: Results of the Cognition and Affect after Stroke - a Prospective Evaluation of Risks study. *Eur stroke J*. 2020;5(1):78-84. doi:10.1177/2396987319883445

40. Zhào H, Liu J, Xia Z, Xie H, Huang Y. Diagnosis and Assessment of Apathy in Elderly Chinese Patients With Cerebral Small Vessel Disease. *Front Psychiatry*. 2021;Aug(3).

41. Mihalov J, Mikula P, Budiš J, Valkovič P. Frontal Cortical Atrophy as a Predictor of Poststroke Apathy. *J Geriatr Psychiatry Neurol*. 2016;29(4):171-176. doi:10.1177/0891988716641248

42. Sarabia-Cobo CM, Pérez V, Hermosilla C, Nuñez MJ, de Lorena P. Apathy and Leukoaraiosis in Mild Cognitive Impairment and Alzheimer's Disease: Multicenter Diagnostic Criteria according to the Latest Studies. *Dement Geriatr Cogn Dis Extra*. 2014;4(2):228-235. doi:10.1159/000363227

43. Jonsson M, Edman Å, Lind K, Rolstad S, Sjögren M, Wallin A. Apathy is a prominent neuropsychiatric feature of radiological white-matter changes in patients with dementia. *Int J Geriatr Psychiatry*. 2010;25(6):588-595. doi:10.1002/gps.2379

44. Staekenborg SS, Su T, Van Straaten ECW, et al. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. *J Neurol Neurosurg Psychiatry*. 2010;81(5):547-551. doi:10.1136/jnnp.2009.187500

45. Delrieu J, Desmidt T, Camus V, et al. Apathy as a feature of prodromal Alzheimer's disease: an FDG-PET ADNI study. *Int J Geriatr Psychiatry*. 2015;30(5):470-477. doi:10.1002/GPS.4161

46. Nebes RD, Vora IJ, Meltzer CC, et al. Relationship of deep white matter hyperintensities and apolipoprotein E genotype to depressive symptoms in older adults without clinical depression. *Am J Psychiatry*. 2001;158(6):878-884. doi:10.1176/APPI.AJP.158.6.878

47. Starkstein SE, Sabe L, Vázquez S, et al. Neuropsychological, psychiatric, and cerebral perfusion correlates of leukoaraiosis in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 1997;63(1):66-73. doi:10.1136/JNNP.63.1.66

48. Manso-Calderón R, Cacabelos-Pérez P, Sevillano-García MD, Herrero-Prieto ME, González-Sarmiento R. The impact of vascular burden on behavioural and psychological symptoms in older adults with dementia: the BEVASDE study. *Neurol Sci*. 2020;41(1):165-174. doi:10.1007/S10072-019-04071-3/TABLES/4

49. Ogawa Y, Hashimoto M, Yatabe Y, et al. Association of cerebral small vessel disease with delusions in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 2013;28(1):18-25. doi:10.1002/GPS.3781

50. Yao H, Takashima Y, Mori T, et al. Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: the Sefuri brain MRI study. *Hypertens Res*. 2009;32(7):586-590. doi:10.1038/HR.2009.65

51. Sonohara K, Kozaki K, Akishita M, et al. White matter lesions as a feature of cognitive impairment, low vitality and other symptoms of geriatric syndrome in the elderly. *Geriatr Gerontol Int*. 2008;8(2):93-100. doi:10.1111/J.1447-0594.2008.00454.X

52. Hirono N, Kitagaki H, Kazui H, Hashimoto M, Mori E. Impact of White Matter Changes on Clinical Manifestation of Alzheimer's Disease. *Stroke*. 2000;31(9):2182-2188. doi:10.1161/01.STR.31.9.2182

53. Starkstein SE, Mizrahi R, Capizzano AA, Acion L, Brockman S, Power BD. Neuroimaging correlates of apathy and depression in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 2009;21(3):259-265. doi:10.1176/JNP.2009.21.3.259

54. Tang WK, Chen YK, Liang HJ, et al. Location of infarcts and apathy in ischemic stroke. *Cerebrovasc Dis*. 2013;35(6):566-571. doi:10.1159/000351152

55. Mihalov J, Mikula P, Budiš J, Valkovič P. Frontal Cortical Atrophy as a Predictor of Poststroke Apathy. doi:10.1177/0891988716641248

56. Tang WK, Chen YK, Liang HJ, et al. Location of infarcts and apathy in ischemic stroke. *Cerebrovasc Dis*. 2013;35(6):566-571. doi:10.1159/000351152

57. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int psychogeriatrics*. 2010;22(3):426-436. doi:10.1017/S1041610209991335

58. Aharon-Peretz J, Kliot D, Tomer R. Behavioral differences between white matter lacunar dementia and Alzheimer's disease: a comparison on the neuropsychiatric inventory. *Dement Geriatr Cogn Disord*. 2000;11(5):294-298. doi:10.1159/000017252

59. Zhang Y, Wu J, Wu W, et al. Reduction of white matter integrity correlates with apathy in Parkinson's disease. *Int J Neurosci*. 2018;128(1):25-31. doi:10.1080/00207454.2017.1347170

60. Zhang Y, Zhang G yong, Zhang Z en, He A qi, Gan J, Liu Z. White matter hyperintensities: a marker for apathy in Parkinson's disease without dementia? *Ann Clin Transl Neurol*. 2020;7(9):1692. doi:10.1002/ACN3.51159

61. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4(2):134-139. doi:10.1176/jnp.4.2.134

62. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2314. doi:10.1212/WNL.44.12.2308

63. Bertens AS, Moonen JEF, de Waal MWM, et al. Validity of the three apathy items of the Geriatric Depression Scale (GDS-3A) in measuring apathy in older persons. *Int J Geriatr Psychiatry*. 2017;32(4):421-428. doi:10.1002/GPS.4484

64. Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, Marin RS. Are the available apathy measures reliable and valid? A review of the psychometric evidence. *J Psychosom Res*. 2011;70(1):73-97. doi:10.1016/J.JPSYCHORES.2010.01.012

65. Walton ME, Bannerman DM, Rushworth MFS. The role of rat medial frontal cortex in effort-based decision making. *J Neurosci*. 2002;22(24):10996-11003. doi:10.1523/JNEUROSCI.22-24-10996.2002

66. Cohen RA, Kaplan RF, Zuffante P, et al. Alteration of intention and self-initiated action associated with bilateral anterior cingulotomy. *J Neuropsychiatry Clin Neurosci*. 1999;11(4):444-453. doi:10.1176/JNP.11.4.444

67. Njomboro P, Deb S, Humphreys GW. Apathy and executive functions: insights from brain damage involving the anterior cingulate cortex. *BMJ Case Rep*. 2012;2012. doi:10.1136/BCR-02-2012-5934

68. Moretti R, Caruso P. An Iatrogenic Model of Brain Small-Vessel Disease: Post-Radiation Encephalopathy. *Int J Mol Sci*. 2020;21(18):1-21. doi:10.3390/IJMS21186506

69. den Brok MGHE, van Dalen JW, van Gool WA, Moll van Charante EP, de Bie RMA, Richard E. Apathy in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2015;30(6):759-769. doi:10.1002/mds.26208

70. Vilalta-Franch J, Calvó-Perxas L, Garre-Olmo J, Turró-Garriga O, López-Pousa S. Apathy syndrome in Alzheimer's disease epidemiology: prevalence, incidence, persistence, and risk and mortality factors. *J Alzheimers Dis*. 2013;33(2):535-543. doi:10.3233/JAD-2012-120913

71. Hölttä EH, Laakkonen ML, Laurila J V., Strandberg TE, Tilvis RS, Pitkälä KH. Apathy: prevalence, associated factors, and prognostic value among frail, older inpatients. *J Am Med Dir Assoc*. 2012;13(6):541-545. doi:10.1016/J.JAMDA.2012.04.005

72. Groeneweg-Koolhoven I, Comijs H, Naarding P, de Waal M, van der Mast R. Apathy in Older Persons With Depression: Course and Predictors: The NESDO Study. *J Geriatr Psychiatry Neurol*. 2016;29(4):178-186.

73. Clarke D, Ko J, Lyketsos C, Rebok G, Eaton W. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr*. 2010;22(5):819-829.

74. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: A transdiagnostic approach. *Nat Rev Neurosci*. 2018;19(8):470-484. doi:10.1038/s41583-018-0029-9

75. Tay J, Lisiecka-Ford DM, Hollocks MJ, et al. Network neuroscience of apathy in cerebrovascular disease. *Prog Neurobiol*. 2020;188. doi:10.1016/j.pneurobio.2020.101785

76. Yuen GS, Gunning-Dixon FM, Hoptman MJ, et al. The salience network in the apathy of late-life depression. *Int J Geriatr Psychiatry*. 2014;29(11):1116-1124. doi:10.1002/GPS.4171

77. Robert G, Bannier E, Comte M, et al. Multimodal brain imaging connectivity analyses of emotional and motivational deficits in depression among women. *J Psychiatry Neurosci*. 2021;46(2):E303-E312. doi:10.1503/JPN.200074

78. Ruthirakuhan M, Herrmann N, Vieira D, Gallagher D, Lanctôt KL. The Roles of Apathy and Depression in Predicting Alzheimer Disease: A Longitudinal Analysis in Older Adults With Mild Cognitive Impairment. *Am J Geriatr Psychiatry*. 2019;27(8):873-882. doi:10.1016/J.JAGP.2019.02.003

79. Bakker TJEM, Duivenvoorden HJ, Van Der Lee J, Trijsburg RW. Prevalence of psychiatric function disorders in psychogeriatric patients at referral to nursing home care--the relation to cognition, activities of daily living and general details. *Dement Geriatr Cogn Disord*. 2005;20(4):215-224. doi:10.1159/000087298

80. Rosenberg GA, Wallin A, Wardlaw JM, et al. Consensus statement for diagnosis of subcortical small vessel disease. *J Cereb Blood Flow Metab*. 2016;36(1):6-25. doi:10.1038/jcbfm.2015.172

81. Gupta D, Kuruvilla A. Vascular parkinsonism: what makes it different? *Postgrad Med J*. 2011;87(1034):829-836. doi:10.1136/POSTGRADMEDJ-2011-130051

82. Graham NL, Emery T, Hodges JR. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. *J Neurol Neurosurg Psychiatry*. 2004;75(1):61-71. doi:10.1016/s0084-3970(08)70286-x

83. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord*. 1993;28(2):117-124. doi:10.1016/0165-0327(93)90040-Q

84. Bertens AS, Foster-Dingley JC, van der Grond J, Moonen JEF, van der Mast RC, Rius Ottenheim N. Lower Blood Pressure, Small-Vessel Disease, and Apathy in Older Persons With Mild Cognitive Deficits. *J Am Geriatr Soc*. 2020;68(8):1811-1817. doi:10.1111/JGS.16465

85. Manera V, Abrahams S, Ag L, et al. Recommendations for the Nonpharmacological Treatment of Apathy in Brain Disorders A R T I C L E I N F O. *Am J Geriatr Psychiatry*. 2020;28:410-420. doi:10.1016/j.jagp.2019.07.014

86. Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S, Lanctôt KL. Pharmacological interventions for apathy in Alzheimer's disease. *Cochrane database Syst Rev*. 2018;5(5). doi:10.1002/14651858.CD012197.PUB2

87. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. *Mov Disord*. 2019;34(2):180-198. doi:10.1002/MDS.27602

88. Ward A. Causal criteria and the problem of complex causation. *Med Heal Care Philos*. 2009;12(3):333-343. doi:10.1007/s11019-009-9182-2

# Chapter 8

## Summary and general discussion

## Scope and objectives

The first three studies **(Part I)** of this dissertation aimed at exploring and describing associations between cardio- and cerebrovascular disease and depression, and whether and how vascular risk and neuroticism affect this relationship. In the subsequent three studies **(Part II)** we looked at associations between cerebrovascular disease, specifically cerebral small vessel disease (CSVD), and apathy. We focused on the relationship between CSVD and apathy in remitted depression and also the concept of vascular apathy was thoroughly evaluated. Since this thesis includes more than a decade of research, in this chapter we will not only summarize and discuss the results of the studies reported on but also add recent relevant findings and consider our findings in the light of this new knowledge. The studies were mostly presented in chronological order to emphasize the development of knowledge and insights derived, which influenced the designs of the subsequent studies and our point of view when evaluating and interpreting the results. For reasons of clarity and legibility, we will discuss the findings of each study immediately after its summary (printed in italics).

## Does late-life depression raise the risk of cerebrovascular disease?

*In the Longitudinal Aging Study Amsterdam, we tested the hypotheses that (1) clinically relevant depressive symptoms are an independent risk factor for incident stroke in cardiac and noncardiac patients and that (2) more chronic and severe depressive symptoms are associated with a higher incidence of stroke (**Chapter 2**). Between 1992 and 2002 a random-sampled community-based cohort of older Dutch people (aged ≥55 years) without a history of stroke (N=2965) was followed for 9 years. The study end point was a first (nonfatal or fatal) stroke, at which point we determined associations with depression, as measured at baseline with the National Institute of Mental Health Diagnostic Interview Schedule and the Center for Epidemiological Studies-Depression Scale (CES-D) by means of multivariate Cox proportional hazards regression analyses of stroke incidence. We also investigated associations between the chronicity and severity of the depressive symptoms and stroke incidence using time-dependent variables. We found that in participants with pre-existent cardiac disease (not in those without such a history) clinically relevant depressive symptoms at baseline (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.17-4.09) and the severity (range, 0-60; HR, 1.08; 95% CI, 1.02-1.13) and chronicity (HR, 3.51; 95% CI, 1.13-10.93) of depressive symptoms during follow-up were associated with stroke. Based on these results, we concluded that pre-existent cardiac disease moderates the association between depressive symptoms and incident stroke and that in cardiac patients, baseline depressive symptoms and both the severity and chronicity of symptoms during follow-up are associated with incident stroke.*

This study was published in 2008 and since then, several replication studies have found more and consistent support for a association between depression and stroke, where a meta-analysis calculated the pooled adjusted HR a 1.45 (95% CI, 1.29-1.63) for total

stroke, with the estimated absolute risk difference associated with depression being 106 cases for total stroke per 100,000 individuals per year [1].

In 2008, we offered several explanations for the depression-stroke association, which are still relevant today. We proposed that depression could aggravate atherosclerosis, which was supported by the dose-response effect that we found. Diminished heart-rate variability during stress [2], altered platelet responses related to serotonin [3] and more heart-rhythm irregularities in depressed patients [4] were mentioned as pathophysiological pathways. Since then, HPA-axis dysfunction, metabolic disease and inflammation have been acknowledged as other possible depression-to-atherosclerosis mechanisms [5].
Additionally, it has been suggested that depression could also lead to stroke as a result of a less healthy lifestyle and diminished adherence to vascular treatment [5].

Today, in 2022, we can add another explanation, since heritability of (ischaemic) stroke is 37.9% [6] and depression and stroke share genetic pathways, where genetic polymorphisms of four genes, methylenetetrahydrofolate reductase (MTHFR) and apolipoprotein E (ApoE) have been shown to be associated with an increased risk of both depression and stroke, while there is also some - although not conclusive - evidence for associations between polymorphisms in angiotensin converting enzyme (ACE) and serum paraoxonase (PON1) with depression [7]. These genetic polymorphisms are related to an immune-inflammatory imbalance, increased oxidative and nitrative stress, dysregulation of lipoprotein and lipid metabolism and changes of cerebrovascular morphology and function [7].

Also in the LASA study, we suggested that a synergistic reciprocal relationship between depression and vascular disease might account for the findings that the association between depression and stroke was observed in individuals with a prior history of cardiac disease only. Cardiac disease and cardiac procedures are now known to be associated with silent cerebral infarcts [8], infarcts that have been related to depression and stroke [89], offering a more concrete explanation. Furthermore, depressive symptoms could also be an indicator of a poor prognosis in cardiac patients because the number of depressive symptoms scored on the CES-D (partly) correlated with the severity of underlying cardiovascular disease [10], while the use of antidepressants could also play a role [5].

Summing up, although in our LASA study the depression-stroke association was mediated by existing cardiac disease, the formerly mentioned meta-analysis reported a pooled association between depression and stroke in cardiac as well as noncardiac patients [1].
These findings illustrate that the likelihood of finding a specific association can be enhanced or diminished by the way study population are defined, since associations are often synergistic or interact with other factors, that are not randomly distributed and may be impossible to fully control for.

## Do neuroticism and vascular disease interact in the risk of depression, or in depressed populations in the risk of stroke?

*In the research presented in **Chapters 3** and **4** we explored interactions between neuroticism and vascular disease in the prediction of stroke and depression. In **Chapter 3**, we hypothesized that the relationship between depression and stroke was based on residual confounding, with generalized atherosclerosis both forming a risk factor for depression as well as for stroke and thus that the association between depression and stroke would be stronger in vascular disease-related depression than it would be in neurotic depression. We examined the influence of low neuroticism and the presence of vascular disease on the relationship between depression and stroke in the LASA population (N=2050) during 9 years of follow-up. The incidence of stroke was determined based on self-report data, data from general practitioners and death certificates. Neuroticism was assessed using the Dutch Personality Questionnaire and depression using the CES-D. Among participants with a history of cardiac disease (N=1649) depression predicted stroke independent of the level of neuroticism (HR: 1.05, 95% CI: 1.01-1.10), whereas in the group without pre-existent cardiac disease depression predicted incident stroke only in individuals with low neuroticism (HR 1.05, 95%: 1.00-1.09) and not in those with high neuroticism. We accordingly suggested that late-life depression in context of low neuroticism is a marker of CSVD.*

*In the Nijmegen Biomedical Study, a population-based survey conducted between 2002 and 2005 reported in **Chapter 4**, we looked at the interplay between vascular disease and neuroticism in the prediction of late-life depression in participants (N=1396) aged 70 and over. As neuroticism enhances the impact of life-events and has been linked to a worse adherence to (vascular) treatment, we hypothesized a positive interaction in which high neuroticism would increase the effect of vascular disease on the risk of depression. Depression was assessed using the CES-D and the level of neuroticism (0-12) was measured by means of the Eysenck Personality Questionnaire. Vascular disease was categorized into four levels based on their relatedness to brain damage, i.e., nonvascular disease or a single risk factor, two or more vascular risk factors without vascular disease, the presence of cardiac disease, and finally, the presence of stroke. The results were different for men and women. In the female respondents neuroticism was a strong predictor of depression (OR: 1.6, 95% CI: 1.4-1.8), while in their male counterparts both cardiac disease and stroke attenuated the predictive value of neuroticism (cardiac disease by neuroticism: OR: 0.8, 95% CI: 0.6-0.9; stroke by neuroticism: OR: 0.8, 95% CI: 0.6-0.96). We suggested that apathy caused by vascular disease might attenuate the effect of neuroticism on the risk of depression.*

A recent study of the neurobiological basis of neuroticism in late-life depression provides these results with more context: compared to findings for neurotic, depressed individuals, in non-neurotic peers a higher volume of non-white matter hypointensities was observed on T1-weighted images, which hypointensities are possibly related to cerebrovascular disease, while frontal volumes were smaller in those with high-level neuroticism. These results suggest that different neural pathways may be involved in different types of late-

life depression and once again these findings link late-life depression in low neurotic populations to cerebrovascular disease [11].
Not part of this thesis, but quite relevant for the interpretation of these results is another study [12] in which our group explored the interplay between subclinical atherosclerotic disease and neuroticism in the prediction of late-life depression in 50-70 year-old participants of the Nijmegen Biomedical Study. A principal component analysis of scores on the Beck Depression Inventory yielded two factors, one representing a cognitive-affective symptom cluster and the other a somatic-affective symptom cluster. Atherosclerotic disease as measured by the intima media thickness of the carotid arteries was only associated with the somatic-affective symptom cluster, where severe atherosclerosis attenuated the association between neuroticism and cognitive-depressive symptoms. This latter finding replicated the results of our earlier study (Chapter 4) and provided more substantial support for the hypothesis that the negative interaction between neuroticism and vascular disease in the prediction of depression might be explained by apathy due to cerebrovascular disease.

An imaging study of older individuals with depression showed that white matter hyperintensities (WMH) and lacunar infarcts - as biomarkers of cerebral small vessel disease- were mainly associated with symptoms of anhedonia, concentration problems, psychomotor retardation, appetite disturbance and motivational problems [13]. When the depressive symptom profiles of three different biological pathways to late-life depression, more specifically vascular disease, inflammation and neurodegeneration, were considered, vascular disease was associated with motivational problems, psychomotor retardation and loss of energy [14]. All of these symptoms were not exclusively associated with vascular disease, however, and could also be a consequence of inflammation (loss of energy) or neurodegeneration (motivational problems, psychomotor retardation) [14].

Together these findings highlight the complexity of the interplay of late-life depression, cerebrovascular disease and other major risk-factors. First, the relationship between cerebrovascular disease and depression might be reciprocal but could also be partly explained by residual confounding in that atherosclerotic disease of the cerebral small vessels might enhance the risk of both depression and stroke (Chapters 2 and 3). Furthermore, in certain populations the vascular pathway to depression might be more prominent and thus more easily detected, while in other populations, such as those characterized by high neuroticism, the vascular route to depression might be slighter or (largely) obscure by interaction effects or due to overshadowing by more important risk factors (Chapters 2,3 and 4). Different aetiological pathways to depression might exert differential effects on the brain morphology and functioning [11]. The vascular pathway is then associated with a specific, although not exclusive, depressive symptom profile, with motivational problems and psychomotor retardation [12 13 14], representing the depressive-executive subtype of depression [15].

## Is apathy in remitted depression related to CSVD?

*Given that the symptoms of the apathy syndrome substantially overlap those of the depressive-executive subtype of depression and the nature and strength of the relationship between CSVD and apathy is being debated, the studies in* ***Chapters 5, 6*** *and* ***7*** *were dedicated to apathy and its relation to CSVD.* ***Chapter 5*** *examined apathy in remitted depression and its relationship to vascular damage in 663 participants (mean age 46.5 years, range 18-86 years) of the Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Study of Depression in Older persons (NESDO). To systematically distinguish between residual depressive symptoms and apathy we performed a principal component analysis, which yielded two apathy factors, amotivation and loss of initiative, and one mood factor. When remission of depression was during follow-up, the associations between vascular risk factors or diseases and the two apathy factors was cross-sectionally evaluated by multivariate linear regression analyses in which we corrected for mood. Neither blood pressure nor ankle brachial index, body mass index, smoking, diabetes mellitus, cardiac disease, or cerebrovascular accidents were associated with either of the two apathy factors after mood had been controlled for. This raises the question whether apathy in remitted depression is aetiologically related to the earlier depressive episode and whether it should be regarded as a residual symptom.*

We were thus unable to establish a vascular pathway to apathy in this mixed-age group having recently recovered from depression, which is in line with the findings in late-life populations with a (severe) previous or current depression [16 17 18], with one exception [19]. These results thereby contradict more consistent findings of a CSVD-apathy association in the general and neurodegenerative populations [20] (see **Chapters 6** and **7**). We suggested that in those who suffer from (severe) depression apathy as a symptom of depression might overshadow other pathways to apathy, where apathy after seemingly successful treatment of depression might in fact be a residual symptom.

## Can silent CSVD cause apathy and is vascular apathy a clinical syndrome?

*The hypothesis that CSVD can cause apathy was further examined in* ***Chapters 6*** *and* ***7****. In chapter 6, 14 general population studies on the relationship between subclinical CSVD and apathy were systematically reviewed. Subclinical CSVD was operationalized as WMH or white matter diffusivity changes, lacunar infarcts, cerebral microbleeds, decreasing cortical thickness, and perivascular spaces. Peripheral proxies for subclinical CSVD were also considered: the ankle brachial index, the intima media thickness, cardio-femoral pulse wave velocity, hypertension, or cardiovascular disease. We found that arterial stiffness and white matter diffusivity were not related to apathy, while the associations with cortical thickness were contradictory. Cross-sectional studies did find evidence of apathy being associated with WMH, cerebral microbleeds, cardiovascular disease, hypertension, and the ankle brachial index. Cardiovascular disease was prospectively associated with apathy. The methodologies of the studies included were too heterogeneous to perform meta-analyses.*

*In **Chapter 7**, the vascular apathy hypothesis was evaluated from a broader perspective. We evaluated the evidence for a pathophysiological mechanism in CSVD that could cause apathy and the evidence for the hypothesis that CSVD can be a sole cause of apathy by the Bradford-Hill criteria to distinguish between association and causation. Pathological, neuroimaging and behavioral studies plausibly and coherently showed that pathophysiologically CSVD can cause lesions in the reward network, which can clinically cause an apathy syndrome. Although observational studies in elderly individuals with depression were inconclusive, studies in healthy older adults, stroke patients and people with cognitive impairment consistently showed an association between CSVD (or WMH as a marker of CSVD) and apathy; a biological gradient was confirmed, as well as a temporal relationship, although the evidence for the latter was still weak. The specificity of this causal relation was low and there were often other contributing factors at play in CSVD patients showing symptoms of apathy, particularly depression and cognitive deterioration. Differentiating between vascular apathy and other apathy syndromes on clinical features was not (yet) possible, and in-depth knowledge about differences in the prognosis and efficacy of treatment options for apathy caused by CSVD and other apathy syndromes was lacking. In conclusion, although a causal relationship between CSVD and apathy was established, CSVD was often not the sole cause of apathy, and we recommend looking for other contributing factors in CSVD patients with apathetic symptoms. We also concluded that it is premature to use the term "vascular apathy" since it refers to a distinct clinical apathy syndrome, where we cannot yet differentiate apathy syndromes.*

## Methodological and research considerations

Of course, there are limitations to the findings of the research reported in this thesis, research considerations to be made and lessons to be learned for future designs.

First, in the three studies presented in Part I, we focused on the relationship between cerebrovascular disease and late-life depression, without considering apathy, where apathy might have been a (residual) confounder. When planning longitudinal aetiological or efficacy studies of late-life depression, we recommend researchers to take apathy into account.

When we specifically took care to distinguish between mood and apathy symptoms (Chapter 5), this yielded unexpected results. We could not establish a CSVD-apathy association in remitted depression as previous studies had done in other populations. Since loss-of-interest, anhedonia and psychomotor retardations are also part of a depressive syndrome, we suggested that apathy in remitted depression might more often than has thus far been recognized be a residual symptom of the depression patients have recovered from. This hypothesis warrants further looking into since depression affects so many people, also in later life, and apathy in depression and remaining apathy in remitted depression are also highly prevalent, with all its serious clinical and societal consequences. "Positive" symptoms of depression, such as a diminished mood, ruminating, negative thinking and suicidal thoughts and behavior have, understandably, been receiving much

attention in depression research, but we make a plea for paying a greater focus on apathy and the motivational symptoms of depression. We accordingly suggest including apathy as a separate outcome measure in intervention studies of depression, to gain more knowledge about which treatment reduces the risk of apathy in remitted depression. Such studies should preferably look at depression across the lifespan to enable researchers to chart the similarities and differences in the symptoms and prognosis of apathy in early- and late-life depression and in early- and late-onset depression.

Another important consideration for future research the findings discussed in this thesis highlight is the complex interactions of the risk-factors for late-life depression, and the ceiling effects that can occur when more than one risk-factor is present. Each risk-factor alone contributes a certain amount to the risk of becoming depressed, but when by an accumulation of risks, the threshold effect is reached, the contribution of each individual factor might not be fully accounted for. Especially in severely symptomatic populations ceiling effect may often obscure clinical research findings [21]. Although in the (near) future we may get more grip on individual risk-factors and their relative contributions and interactions by advances in statistics and big-data analyses, at this point our capabilities in predicting late-life depression in the individual are still limited. We are, however, able to identify the most determining risk-factors for late life-depression in well-defined populations, which information is particularly relevant for the development and implementation of dedicated prevention trials. If populations with a high vascular risk would profit from different depression-prevention methods than populations with a high risk because of high neuroticism is yet unknown. More differentiation not only in treatment options for depression, but also in prevention methods could pave the way to better outcomes.

As to the CSVD-apathy relationship, there are still important gaps in our knowledge, where particularly prospective designs in which the progress of CSVD is studied in relation to the course of apathy over time are lacking. Moreover, in addition to depression and cognition, we recommend to include apathy as an outcome measure of brain health in intervention trials in patients with CSVD.

## Considerations for clinical practice

What lessons can physicians learn from the research reported in this thesis? The first ´take-home message' is that the relationship between cerebrovascular disease and late-life depression is bi-directional. The clinician is recommended to pay attention to the presence of vascular risks and vascular disease in older people going through a depression, but to likewise check for the presence of depression in older patients diagnosed with cerebrovascular disease. However, the clinical implication of these findings is as yet limited since the treatment of cerebrovascular disease in people coping with late-life depression does not differ from the general treatment of cerebrovascular disease, which also holds for the treatment of depression resulting from cerebrovascular disease. We also point to the risk of tunnel-vision when cerebrovascular disease is present. Cerebrovascular

disease should not overshadow other factors, such as high neuroticism, that may just as well or even more so underlie or maintain late-life depression. Research models for late-life depression may guide clinicians but they are no substitute for a thorough clinical assessment and analysis of all the risk-factors, sustaining and protective factors involved in the onset, treatment or (relapse) prevention of depression for each individual patient.

Another important consideration for the physician treating older patients for apathy and depression, is that apathy in remitted depression was not significantly associated with CSVD (Chapter 5). This finding once more underscores the similarities between apathy and motivational symptoms of depression, prompting the question whether in remitted depression apathy might be a residual symptom. The etiology of apathy in depression and its treatment is not well understood. Should we recommend antidepressant treatment, further psychotherapy or structured daily activities, or all three? To date, research has not provided much support for one strategy or the other, but since the consequences of apathy can be wide-ranging, we would advise against therapeutic nihilism.

In the general population and in populations with neurodegenerative diseases a causal association between CSVD and apathy was established in chapter 5 and 6. This information might help clinicians, their patients, and the caregivers of their patients, to understand and accept the presence of apathy in CSVD. However, once again, we would not recommend tunnel vision since apathy can have many causes, and in particularly often coincides with depression and cognitive impairment in elderly populations. Therefore, also in CSVD we would recommend the clinician to perform a broad analysis of all the other risk-factors and protective factors for each individual who suffers from apathy.

Finally, we would like to remind clinicians seeing patients with late-life depression and apathy of the many gaps in our current knowledge, most particularly the lack of dedicated treatments for CSVD- or depression-related apathy, and urge them to join researchers in their quest by informing patients and their spouses or caregivers of research programs they might be willing to participate in.

## Considerations for the training of the next generation of psychiatrists:

For those who train the next generation of psychiatrists our findings underscore the importance of epidemiology in the psychiatrist's practice, where psychiatrists should be enabled to estimate the probability and relevance of age-specific risks of late-life depression and for apathy in a diversity of populations. They should learn about CSVD and how CSVD can alter motivational functioning, to thus help them interpret the symptoms they observe in their patients better, but equally or even more importantly, they should be trained in communicating this information to their patients and their partners, family or caregivers.

They need to be informed about the limitations of the current disease models for late-life depression and apathy, and about the fact that more often than not multiple risk-factors

co-occur that interact with and influence each other. With this in mind, they will be able to present their disease model for the individual patient as a (likely) possibility and keep an open mind for different etiologies.

In conclusion, the studies brought together in this thesis emphasizes the importance of apathy, or motivational symptoms, in CSVD and in depression. Whether they will be treating younger or older patients, we recommend that the next generation of psychiatrists are trained to actively ask patients or their partners/caregivers for symptoms of apathy, particularly in those with confirmed CSVD and a current or past depression and, when apathy is present, to discuss the likelihood of a specific disease model and propose a patient-specific treatment.

## References


1. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA*. 2011;306(11):1241-1249. doi:10.1001/JAMA.2011.1282
2. Schiweck C, Piette D, Berckmans D, Claes S, Vrieze E. Heart rate and high frequency heart rate variability during stress as biomarker for clinical depression. A systematic review. *Psychol Med*. 2019;49(2):200-211. doi:10.1017/S0033291718001988
3. Williams MS, Ziegelstein RC, McCann UD, Gould NF, Ashvetiya T, Vaidya D. Platelet Serotonin Signaling in Patients With Cardiovascular Disease and Comorbid Depression. *Psychosom Med*. 2019;81(4):352-362. doi:10.1097/PSY.0000000000000689
4. Shi S, Liu T, Liang J, Hu D, Yang B. Depression and Risk of Sudden Cardiac Death and Arrhythmias: A Meta-Analysis. *Psychosom Med*. 2017;79(2):153-161. doi:10.1097/PSY.0000000000000382
5. Penninx BWJH. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev*. 2017;74:277-286. doi:10.1016/J.NEUBIOREV.2016.07.003
6. Bevan S, Traylor M, Adib-Samii P, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genomewide associations. *Stroke*. 2012;43(12):3161-3167. doi:10.1161/STROKEAHA.112.665760
7. Zhao F, Yue Y, Jiang H, Yuan Y. Shared genetic risk factors for depression and stroke. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;93:55-70. doi:10.1016/J.PNPBP.2019.03.003
8. Hassell MEC, Piek JJ, Delewi R, et al. Silent cerebral infarcts associated with cardiac disease and procedures. *Nat Rev Cardiol*. 2013;10:696-706. doi:10.1038/nrcardio.2013.162
9. Rensma SP, van Sloten TT, Launer LJ, Stehouwer CDA. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2018;90:164-173. doi:10.1016/J.NEUBIOREV.2018.04.003
10. Contrada RJ, Boulifard DA, Idler EL, Krause TJ, Labouvie EW. Course of depressive symptoms in patients undergoing heart surgery: confirmatory analysis of the factor pattern and latent mean structure of the Center for Epidemiologic Studies Depression Scale. *Psychosom Med*. 2006;68(6):922-930. doi:10.1097/01.PSY.0000244391.56598.10
11. Joseph C, Wang L, Wu R, Manning KJ, Steffens DC. Structural brain changes and neuroticism in late-life depression: a neural basis for depression subtypes. *Int psychogeriatrics*. 2021;33(5):515-520. doi:10.1017/S1041610221000284
12. Marijnissen RM, Bus BAA, Schoevers RA, et al. Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry*. 2014;22(8):801-810. doi:10.1016/j.jagp.2013.01.001

13. Grool AM, Van Der Graaf Y, Mali WPTM, Witkamp TD, Vincken KL, Geerlings MI. Location and progression of cerebral small-vessel disease and atrophy, and depressive symptom profiles: the Second Manifestations of ARTerial disease (SMART)-Medea study. *Psychol Med*. 2012;42(2):359-370. doi:10.1017/S0033291711001383

14. Naarding P, Schoevers RA, Janzing JGE, Jonker C, Koudstaal PJ, Beekman ATF. A study on symptom profiles of late-life depression: the influence of vascular, degenerative and inflammatory risk-indicators. *J Affect Disord*. 2005;88(2):155-162. doi:10.1016/J.JAD.2005.07.002

15. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. *J Gerontol A Biol Sci Med Sci*. 2017;72(3):343-352. doi:10.1093/GERONA/GLW241

16. Carlier A, van Exel E, Dols A, et al. The course of apathy in late-life depression treated with electroconvulsive therapy; a prospective cohort study. *Int J Geriatr Psychiatry*. 2018;33(9):1253-1259. doi:10.1002/gps.4917

17. Oudega ML, Siddiqui A, Wattjes MP, et al. Are Apathy and Depressive Symptoms Related to Vascular White Matter Hyperintensities in Severe Late Life Depression? *J Geriatr Psychiatry Neurol*. 2021;34(1):21-28. doi:10.1177/0891988720901783

18. Lampe IK, Heeren TJ. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *Int psychogeriatrics*. 2004;16(4):481-486. doi:10.1017/S1041610204000766

19. Yuen GS, Gunning FM, Woods E, Klimstra SA, Hoptman MJ, Alexopoulos GS. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *J Affect Disord*. 2014;166:179-186. doi:10.1016/j.jad.2014.05.008

20. Clancy U, Gilmartin D, Jochems ACC, Knox L, Doubal FN, Wardlaw JM. Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis. *The lancet Psychiatry*. 2021;8(3):225-236. doi:10.1016/S2215-0366(20)30431-4

21. Liu Q, Wang L. t-Test and ANOVA for data with ceiling and/or floor effects. *Behav Res Methods*. 2021;53(1):264-277. doi:10.3758/S13428-020-01407-2

# Appendices



# Nederlandse wetenschappelijke samenvatting

## Introductie

### Depressie op latere leeftijd

Depressie op latere leeftijd is een vaak voorkomende aandoening met een prevalentie van 0.9-9.4% voor zelfstandig wonende ouderen en 14-42% voor ouderen die wonen in een instelling[1]. Klinisch relevante depressieve symptomen (zonder dat volledig aan de criteria voor een depressieve stoornis voldaan wordt) komen zelfs nog vaker voor [2]. De gevolgen van een depressieve stoornis of depressieve symptomen op latere leeftijd kunnen ernstig zijn. Er wordt door depressieve ouderen meer gebruik gemaakt van gezondheidszorg, er is vaker sprake van functionele of cognitieve beperkingen en de kwaliteit van leven wordt als minder goed ervaren. Daarnaast verhoogt een depressie op oudere leeftijd het sterftecijfer [3], wat voor een deel verklaard wordt door een hogere sterfte aan cardiovasculaire [4 5] en cerebrovasculaire ziekte[6]. Deze laatste bevinding stimuleerde het wetenschappelijke onderzoek naar de mogelijke oorzakelijke verbanden tussen depressie en cardio- en cerebrovasculaire ziekte[7]. Waarbij de verhoogde kans op depressie na een hartinfarct[8] of beroerte[9] die ook gevonden werd, wees op een bidirectionele relatie.

MRI-studies lieten een verband zien tussen witte stofafwijkingen (WMH), wat wijst op het bestaan van ziekte van de kleine vaten van de hersenen (cerebral small vessel disease, CSVD) en depressie [10]. Klinisch werd met CSVD samenhangende-depressie in verband gebracht met executieve functiestoornissen en therapieresistentie, wat leidde tot de vasculaire depressie hypothese[11]. Echter: de naam 'vasculaire depressie' werd later weer verlaten, omdat een oorzakelijke relatie en een specifiek klinisch syndroom beide niet afdoende konden worden vastgesteld [12 13]. Hoewel het verband tussen WMH en depressie bevestigd werd in een meta-analyse [10], zijn WMH vooral gerelateerd aan items in depressieschalen die wijzen op motivatieproblemen, zoals interesseverlies en psychomotore vertraging [14]. Daarom werd in latere studies gesuggereerd dat CSVD mogelijk sterker samenhangt met apathie dan met depressie [15 16].

*Apathie*

Apathie is een transdiagnostisch symptoom dat bij verschillende neurologische en psychiatrische ziekten gezien wordt [17], maar het kan ook een op zichzelf stand syndroom zijn. Apathie wordt gekarakteriseerd door verminderde activiteit, minder gedachten en minder emoties. Net als depressie, kan apathie ernstige gevolgen hebben: het vermindert de kwaliteit van leven [18], vergroot de kans op functionele beperkingen [19] en vormt een hoge belasting voor mantelzorgers [20 21]. Apathie verhoogt de kans op cardiovasculaire ziekte, beroerte en sterfte[22]. Daarnaast is apathie gerelateerd aan dementie [23].

Recent zijn consensus criteria voor apathie vastgesteld, die gebruikt kunnen worden in gezonde en ook in neuropsychiatrisch zieke populaties [24]. Bij gebruik van deze criteria blijkt de prevalentie van apathie 55% bij de ziekte van Alzheimer, 70% bij gemengde dementie, 43% bij beperkte cognitieve stoornissen, 27% bij de ziekte van Parkinson, 53% bij schizofrenie en 94% bij een depressieve stoornis [17].

## De vasculaire apathie hypothese

De prevalentie van apathie bij CSVD is hoog, namelijk 52%, en het verband tussen CSVD en apathie is onafhankelijk van depressie vastgesteld. De vasculaire apathie hypothese stelt dat CSVD apathie kan veroorzaken door het beschadigen van fronto-striatale verbindingen in de hersenen [25] [26] [27]. Is CSVD inderdaad een mogelijke oorzakelijke factor bij apathie? Kan CSVD als enkele factor apathie veroorzaken? Vormt CSVD-gerelateerde apathie een herkenbaar en af te grenzen klinisch syndroom, zoals door de term 'vasculaire apathie' gesuggereerd wordt?

## Onderzoeksthema's en doelstellingen

De relaties tussen (cerebro)vasculaire ziekte en depressie en apathie vormen het kernthema van dit proefschrift.
In de eerste drie studies **(Deel I)** van dit proefschrift worden de associaties tussen cardio- en cerebrovasculaire ziektes en depressie geëxploreerd en beschreven. Ook wordt onderzocht hoe de aanwezigheid van vasculaire risicofactoren en/of neuroticisme het verband tussen cerebrovasculaire ziekte en depressie beïnvloedt.

In de daaropvolgende drie studies **(Deel II)** worden associaties tussen cerebrovasculaire ziekte, en met name tussen ziekte van de kleine vaten van de hersenen (cerebral small vessel disease, CSVD) en apathie onderzocht. Ook wordt apathie en het verband tussen CSVD en apathie na herstel van depressie bestudeerd. Tenslotte wordt de wetenschappelijke basis en de reikwijdte van de 'vasculaire apathie hypothese' onderzocht.

### Deel I

- In **hoofdstuk 2** wordt onderzocht of depressie bij oudere personen met en zonder hartziekte geassocieerd is met een verhoogd risico op beroerte.
- In **hoofdstuk 3** wordt onderzocht of het verhoogde risico op beroerte bij depressie anders is bij onderliggende vasculaire ziekte dan bij een hoog niveau van neuroticisme. Hierbij is de hypothese dat het verhoogde risico op beroerte wél wordt gezien bij onderliggende vasculaire ziekte en niet bij een hoog niveau van neuroticisme.
- In de studie beschreven in **hoofdstuk 4** werd geëxploreerd of neuroticisme en vasculaire ziekte interacteren als risicofactoren voor depressie.

### Deel II

- In **hoofdstuk 5** wordt onderzocht of apathie na herstel van depressie samenhangt met CSVD, ook als gecorrigeerd wordt voor persisterende stemmingsproblemen.
- **Hoofstuk 6** betreft een systematische review van studies die onderzoeken of subklinische CVSD samenhangt met apathie in de algemene bevolking.
- De laatste studie, beschreven in **hoofdstuk 7**, exploreert of CSVD een (op zichzelf staande) oorzaak van apathie kan zijn. Ook wordt in dit hoofdstuk onderzocht of ´vasculaire apathie´ voldoet aan de criteria voor een klinisch syndroom, en of de term ´vasculaire apathie´ eigenlijk wel gebruikt zou moeten worden in de klinisch praktijk.

Omdat dit proefschrift meer dan 10 jaar onderzoek behelst, zullen we in dit hoofdstuk niet alleen de studies samenvatten maar ook op de resultaten reflecteren in het licht van recentere wetenschappelijke bevindingen. De studies worden zoveel mogelijk in chronologische volgorde weergegeven om de ontwikkeling van kennis en inzichten zichtbaar te maken. Om de leesbaarheid en de helderheid van dit hoofdstuk te bevorderen worden de samenvattingen van de studies schuin weergegeven en steeds direct gevolgd door een evaluatie van de bevindingen.

# Deel I

**Verhoogt een depressie op latere leeftijd de kans op cerebrovasculaire ziekte?**

*In de Longitudinal Aging Study Amsterdam werden de volgende hypothesen getoetst: (1) dat klinisch relevante depressieve symptomen een onafhankelijke risicofactor vormen voor het krijgen van een beroerte in patiënten met en zonder hartziekte, en (2) dat meer chronische en ernstigere depressieve symptomen geassocieerd zijn met een hogere kans op een beroerte* ***(Hoofdstuk 2).***

*Tussen 1992 en 2002 werd een random samengesteld cohort uit de algemene bevolking van Nederlanders met een leeftijd van 55 jaar of ouder (zonder een voorgeschiedenis van beroerte) (N=2965) gevolgd gedurende 9 jaar. Eindpunt van de studie was het doormaken van een eerste (fatale of niet-fatale) beroerte. De associatie tussen depressie op het beginpunt van de studie, welke werd vastgesteld met behulp van the National Institute of Mental Health Diagnostic Interview Schedule en de Center for Epidemiological Studies-Depressie schaal (CES-D), en de incidentie van beroerte werd berekend met behulp van multivariate Cox proportional hazards regressieanalyse. Ook onderzochten we het verband tussen de chroniciteit en de ernst van depressieve symptomen en de incidentie van beroerte met behulp van tijdsafhankelijke variabelen. De resultaten lieten zien dat in studiedeelnemers met een voorgeschiedenis van hartziekte (en niet in degenen zonder deze voorgeschiedenis) klinisch relevante depressieve symptomen op het beginpunt (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.17-4.09) geassocieerd waren met de kans op het ontstaan van een beroerte. Er was ook een associatie tussen de ernst (range, 0-60; HR, 1.08; 95% CI, 1.02-1.13) en chroniciteit (HR, 3.51; 95% CI, 1.13-10.93) van depressieve symptomen gedurende follow-up met de kans op het ontstaan van een beroerte.*

*Op basis van deze resultaten, concludeerden we dat de aanwezigheid van een hartziekte invloed had op de mate van het verband tussen depressieve symptomen en het ontstaan van een beroerte; en dat in hartpatiënten niet alleen depressieve symptomen aan het begin van de studie, maar ook de ernst en chroniciteit van de symptomen gedurende de studie samenhingen met een hoger risico op het ontstaan van een beroerte.*
Deze studie werd gepubliceerd in 2008 en sindsdien werden de resultaten in meerdere replicatie-studies bevestigd. Ook werd de associatie tussen depressie en het ontstaan van een beroerte vastgesteld in populaties zonder hartziekte. Een meta-analyse berekende een gepoolde aangepaste HR van 1.45 (95% CI, 1.29-1.63) voor beroerte, met een geschat

absoluut risicoverschil bij depressie van 106 gevallen van beroerte per 100.000 personen per jaar [6].

In 2008 waren er meerdere nog steeds relevante verklaringen voor het verband tussen depressie en beroerte. Depressie zou atherosclerose kunnen verergeren, een verklaring die gesteund werd door de gevonden dosis-effect relatie. Andere pathofysiologische verklaringen waren: een verminderde variabiliteit van het hartritme tijdens stress [30], veranderde reacties van de bloedplaatjes samenhangend met serotonine [31] en de aanwezigheid van meer verstoringen van het hartritme bij depressieve patiënten [32]. Sindsdien zijn ook een dysfunctie van de HPA-as, metabole ziekte en ontsteking erkende mechanismes die bijdragen aan het ontstaan of verergeren van atherosclerose bij depressie [33]. Daarnaast kan depressie ook de kans op een beroerte verhogen door een minder gezonde leefstijl en een verminderde compliance aan behandelvoorschriften voor vaatziektes [33].

Nu, in 2022, is er nog een verklaring, omdat de erfelijkheid van (ischemische) beroerte 37.9%[34] bedraagt en depressie en beroerte gemeenschappelijke genetische routes delen. Genetische polymorfismes van twee genen, methyleentetrahydrofolaat reductase (MTHFR) en apolipoproteine E (ApoE) zijn in verband gebracht met een verhoogd risico op depressie en beroerte, en polymorfismes van twee andere genen, angiotensine converting enzym (ACE) en serum paraoxonase (PON1) zijn mogelijk geassocieerd met depressie [35]. Deze genetische polymorfismes houden verband met een dysbalans tussen immuniteit en ontstekingsmechanismes, verhoogde oxidatieve en nitratieve stress, dysregulatie van lipoproteine en lipide metabolisme en veranderingen in cerebrovasculaire morfologie en functie [35].

In de beschreven LASA-studie werd geopperd, dat er een synergistische reciproke relatie tussen depressie en vaatziekte zou kunnen bestaan, die zou verklaren waarom de associatie tussen depressie en beroerte alleen in hartpatiënten werd gevonden. Hartziekte en hartoperaties zijn geassocieerd met stille beroertes [36], en deze stille beroertes zijn geassocieerd met depressie en symptomatologische beroerte [36] [10]. Bovendien kunnen depressieve symptomen een indicator zijn voor een slechtere prognose in hartpatiënten omdat het aantal depressieve symptomen (vastgesteld met behulp van de CES-D) gecorreleerd is aan de ernst van de onderliggend hartvaatziekte [37]. Ook het gebruik van antidepressiva zou een rol kunnen spelen[33].
Uiteindelijk werd in een latere meta-analyse onafhankelijk van hartziekte een gepoold verband tussen depressie en beroerte vastgesteld, hoewel in de LASA-studie het verband tussen depressie en beroerte werd beïnvloed door de aanwezigheid van hartziekte [6]. Deze bevindingen laten zien dat de kans om een verband wel of niet vast te stellen in een studie beïnvloed wordt door de eigenschappen van de bestudeerde populatie, aangezien statistische verbanden door interactie met andere factoren vergroot of verkleind kunnen worden. En dergelijke interactiefactoren zijn niet random verdeeld over de bevolking en vaak niet volledig te controleren.

**Spelen interacties tussen de aanwezigheid van neuroticisme en vasculaire ziekte een rol in het risico op depressie, of in depressieve populaties in het risico op beroerte?**

*In het onderzoek dat gepresenteerd wordt in **Hoofdstuk 3** en **4** werden interacties tussen neuroticisme en vasculaire ziekte bij het voorspellen van beroerte en depressie geëxploreerd. In **Hoofdstuk 3** werd de hypothese dat in het verband tussen depressie en beroerte 'residual confounding' een rol speelt onderzocht, waarbij gegeneraliseerde atherosclerose een risicofactor vormt voor beiden (depressie en beroerte). Er werd gesteld dat hierdoor het verband tussen depressie en beroerte groter zou zijn in aan vasculaire ziekte-gerelateerde depressie dan in neurotische depressie.*

*De invloed van laag neuroticisme en de aanwezigheid van vasculaire ziekte op het verband tussen depressie en beroerte werd bestudeerd in de LASA-populatie (N=2050) gedurende 9 jaar follow-up. De incidentie van beroerte werd vastgesteld met behulp van anamnestische informatie, informatie van huisartsen en verklaringen van overlijden. Neuroticisme werd gemeten met behulp van de Dutch Personality Questionnaire en depressie met behulp van de CES-D. In deelnemers met een voorgeschiedenis van hartziekte (N=1649) was depressie een voorspeller voor beroerte, een bevinding die onafhankelijk was van het niveau van neuroticisme (HR: 1.05, 95% CI: 1.01-1.10). In deelnemers zonder hartziekte was depressie alleen in individuen met een laag neuroticisme-niveau een voorspeller voor beroerte (HR 1.05, 95%: 1.00-1.09). Op basis van deze bevindingen suggereerden we dat depressie op oudere leeftijd bij een laag niveau van neuroticisme een marker zou kunnen zijn van ziekte van de kleine vaten van de hersenen, CSVD.*

*In de Nijmegen Biomedical Study (2002-2005), een studie waarbij diverse vragenlijsten werden afgenomen in de algemene bevolking, werd de interactie tussen vasculaire ziekte en neuroticisme bij het voorspellen van depressie op oudere leeftijd (N=1397, leeftijd >70 jaar) bestudeerd. De bevindingen worden in **Hoofstuk 4** van dit proefschrift beschreven. Omdat neuroticisme de impact van life-events vergroot en omdat neuroticisme geassocieerd is met een slechtere compliance aan vasculaire behandelingen, werd de hypothese geponeerd dat er een positieve interactie tussen neuroticisme en vasculaire ziekte zou bestaan in het voorspellen van depressie. In andere woorden: dat een hoog niveau van neuroticisme het risico op depressie in deelnemers met vasculaire ziekte zou verhogen.*

*Depressie werd gemeten met behulp van de CES-D en het niveau van neuroticisme (0-12) werd gemeten met behulp van de Eysenck Personality Questionnaire. Vasculaire aandoeningen werd ingedeeld in vier categorieën, gebaseerd op de relatie met hersenschade, namelijk (1) geen vasculaire ziekte of een enkele risicofactor, (2) twee of meer vasculaire risicofactoren zonder ziekte, (3) hartziekte en (4) beroerte. De resultaten waren voor mannen en vrouwen verschillend. In vrouwelijke deelnemers was neuroticisme een sterke voorspeller voor depressie (OR: 1.6, 95% CI: 1.4-1.8), terwijl in mannelijke deelnemers hartziekte en beroerte de voorspellende waarde van neuroticisme verminderden (hartziekte en neuroticisme: OR: 0.8, 95% CI: 0.6-0.9; beroerte en neuroticisme: OR: 0.8, 95% CI: 0.6-0.96). Een verklaring hiervoor zou kunnen zijn dat*

*apathie veroorzaakt door vasculaire ziekte het depressogene effect van neuroticisme vermindert.*

Een recente studie waarin de neurobiologie van neuroticisme bij depressie op latere leeftijd werd onderzocht biedt meer context aan deze resultaten: in niet-neurotische depressieve deelnemers werd een hoger volume aan niet-witte stofafwijkingen gezien in T1-gewogen beeldvorming dan bij hoog-neurotische deelnemers. Deze afwijkingen worden gerelateerd aan cerebrovasculaire ziekte. In hoog-neurotische depressieve deelnemers waren kleinere frontale volumes in de hersenen te zien. Deze resultaten laten zien dat mogelijk verschillende neurale routes een rol spelen in verschillende types van depressie op latere leeftijd. En deze resultaten leggen ook opnieuw een verband tussen cerebrovasculaire ziekte en depressie op oudere leeftijd in laag-neurotische populaties [38].

In een andere studie, werd de interactie tussen subklinische atherosclerose en neuroticisme bij het voorspellen van depressie in 50-70 jarige deelnemers van de Nijmegen Biomedical Study[26] geëxploreerd. Met behulp van een principale component analyse op de scores van de Beck Depression Inventory werden twee factoren gevonden, waarbij de ene factor een cognitief-affectief cluster van symptomen en de andere een somatisch-affectief cluster van symptomen vertegenwoordigt. Atherosclerose, weergegeven door de intima media dikte (IMT) van de carotiden, was enkel geassocieerd met het somatisch-affectieve cluster. Bovendien verminderde ernstige atherosclerose de associatie tussen neuroticisme en cognitief-affectieve symptomen. Deze laatste bevinding repliceerde de bevindingen van de in **Hoofstuk 4** beschreven studie en gaf meer steun aan de hypothese dat de negatieve interactie tussen neuroticisme en vasculaire ziekte bij de voorspelling van depressie mogelijk verklaard wordt door apathie veroorzaakt door cerebrovasculaire ziekte.

Beeldvormend onderzoek naar depressie op oudere leeftijd toonde aan dat witte stofafwijkingen (WMH) en lacunaire infarcten, -beiden biomarkers voor CSVD- vooral geassocieerd waren met symptomen van anhedonie, concentratieproblemen, psychomotore retardatie, eetluststoornissen en motivatieproblemen[14]. Als de symptoomprofielen van depressie op latere leeftijd vergeleken werden tussen drie verschillende biologische routes naar depressie, namelijk vasculaire ziekte, inflammatie en neurodegeneratie, was vasculaire ziekte geassocieerd met motivatieproblemen, psychomotore retardatie en een verminderd energieniveau[39]. Deze symptomen waren echter niet exclusief geassocieerd met aan vasculaire ziekte gerelateerde-depressie, maar kwamen ook voor bij inflammatie (een verminderd energieniveau) en neurodegeneratie (motivatieproblemen, psychomotore retardatie)[39].

Al deze bevindingen illustreerden de complexiteit van het samenspel tussen cerebrovasculaire ziekte, depressie en andere factoren, zoals atherosclerose en neuroticisme.

Wat kunnen we hier verder uit opmaken? Ten eerste, de relatie tussen cerebrovasculaire ziekte en depressie werkt mogelijk twee kanten op, maar kan ook deels verklaard worden door 'residual confounding' waarbij atherosclerose van de kleine vaten van de

hersenen het risico op depressie en beroerte beide verhoogt (**Hoofdstukken 2 en 3**). Daarnaast kan de vasculaire route naar depressie in bepaalde populaties makkelijker vastgesteld worden, terwijl in andere populaties, zoals in hoog-neurotische populaties, de vasculaire route moeilijker aan te tonen is door interactie-effecten of doordat deze route overschaduwd wordt door andere sterke(re) risicofactoren (**Hoofdstukken 2, 3 en 4**). En: verschillende etiologische routes naar depressie gaan mogelijk samen met verschillende effecten op de morfologie en het functioneren van het brein[38]. De vasculaire route is dan geassocieerd met een specifiek, maar niet exclusief, depressief symptoom-profiel, met motivatieproblemen en psychomotore retardatie [26 14 39], ook wel het depressieve-executieve subtype van depressie genoemd [40].

## Deel II

**Is er een verband tussen apathie na herstel van depressie en CSVD?**

*Omdat de symptomen van apathie veel overeenkomsten vertonen met die van het depressieve-executieve subtype van depressie en omdat er discussie is over de aard en de aanwezigheid van een relatie tussen CSVD en apathie, gaan de studies in* ***Hoofstukken 5, 6 en 7*** *over apathie en de relatie tussen CSVD en apathie.*

*In* ***Hoofdstuk 5*** *werd apathie na herstel van depressie bestudeerd, waarbij de hypothese was dat apathie na herstel van depressie samen zou hangen met ziekte van de kleine vaten van de hersenen, CSVD.*

*Dit werd onderzocht in 663 deelnemers (gemiddelde leeftijd 46.5 jaar, variërend van 18-86 jaar) van de Netherlands Study of Depression and Anxiety (NESDA) en de Netherlands Study of Depression in Older persons (NESDO). Om restsymptomen van depressie grondig te onderscheiden van apathie werd een principale component analyse uitgevoerd, die twee apathie factoren opleverde, amotivatie en verlies van initiatief, en een stemmingsfactor. Als er sprake was van een herstelde depressie werden de associaties tussen vasculaire risicofactoren of vasculaire ziektes en apathie (de totale apathiescore of de apathiefactoren) cross-sectioneel onderzocht met behulp van multivariate lineaire regressieanalyse, gecontroleerd voor de stemming. Geen van de vasculaire risicofactoren (hoge bloeddruk, enkel-arm index, roken, diabetes mellitus) en geen van de vasculaire ziektes (hartziekte of cerebrovasculaire ziekte) waren geassocieerd met apathie of de apathiefactoren nadat gecontroleerd was voor de stemming. Dit roept de vraag op of apathie na herstel van depressie mogelijk eerder gerelateerd is aan de eerdere depressieve episode, en dan mogelijk als een restsymptoom beschouwd moet worden.*

Er werd dus geen vasculaire route naar apathie vastgesteld in deze groep deelnemers van gemengde leeftijd, die recent hersteld was van depressie. Dit strookt met de negatieve resultaten die werden gevonden in oudere populaties die recent hersteld waren van een (ernstige) depressie of nog depressief waren [41 42 43], al was er ook een studie met positieve resultaten [44]. In de algemene populatie of in neurodegeneratieve populaties werden meer consistent associaties tussen CSVD en apathie gevonden [45] (zie ook **Hoofdstukken 6**

en **7**). Mogelijk is het zo dat in diegenen die lijden aan (ernstige) depressie, apathie na ogenschijnlijk succesvolle behandeling van depressie in feite toch kan samenhangen met de eerdere depressie en misschien zelfs een restsymptoom kan zijn.

**Kan subklinische CSVD apathie veroorzaken en is vasculaire apathie een eigenstandig klinisch syndroom?**

*De hypothese dat CSVD apathie kan veroorzaken werd verder onderzocht in **Hoofdstukken 6** en **7**. **Hoofdstuk 6** betrof een systematische review van 14 studies die werden verricht in de algemene bevolking waarin de relatie tussen subklinische CSVD en apathie werd onderzocht. Subklinische CSVD werd geoperationaliseerd als WMH of afwijkingen in de diffusie van de witte stof, als lacunaire infarcten, cerebrale microbloedingen, verminderde corticale dikte en/of perivasculaire ruimtes. Perifere proxies (afgeleide maten) voor subklinische CSVD werden ook bestudeerd: de enkel-arm index, de intima-media dikte, de cardio-femorale polsgolfsnelheid, hypertensie, of cardiovasculaire ziekte. We vonden dat arteriële stijfheid en diffusie van de witte stof niet geassocieerd waren met apathie, en dat de beschreven associaties met corticale dikte inconsistent waren. Cross-sectionele studies toonden wel een verband tussen apathie en WMH, cerebrale microbloedingen, cardiovasculaire ziekte, hypertensie en de enkel-arm index aan. Cardiovasculaire ziekte was in prospectief onderzoek gerelateerd aan apathie. De methoden die de studies gebruikten waren te heterogeen om een meta-analyse uit te voeren.*

*In **Hoofdstuk 7** werd de vasculaire apathy hypothese vanuit verschillende invalshoeken bekeken in een uitgebreide sterkte-zwakte analyse. Het bewijs voor het bestaan van een pathofysiologisch mechanisme bij CSVD dat apathie kan veroorzaken werd onderzocht, net zoals het bewijs voor de hypothese dat CSVD een op zichzelf staande veroorzaker van apathie kan zijn. De Bradford-Hill criteria om onderscheid te maken tussen een verband en een oorzaak werden hiervoor gebruikt. Pathologie-, beeldvorming- en gedragsstudies lieten geloofwaardig en coherent zien dat CSVD schade kan veroorzaken in het beloningsnetwerk (reward network) in de hersenen, wat klinisch een apathiesyndroom kan veroorzaken. En hoewel geen duidelijke conclusies getrokken konden worden uit studies tijdens en na depressie, lieten studies in gezonde ouderen, studies na een beroerte en studies in deelnemers met cognitieve stoornissen consistente associaties zien tussen CSVD (of WMH als biomarker van CSVD) en apathie. Er werd een dosis-respons effect gezien, en ook een tijdsrelatie, alhoewel het bewijs voor een tijdsrelatie nog zwak werd gevonden. De specificiteit van deze oorzakelijke relatie was laag, vaak waren er andere bijdragende factoren die een rol speelden in het veroorzaken van apathie in CSVD-patiënten, zoals depressie of cognitieve achteruitgang.*

*Het bleek nog niet mogelijk om onderscheid te maken tussen vasculaire apathie en andere apathiesyndromen op basis van symptoomprofielen, en er was nog geen kennis over verschillen in prognose of behandeleffectiviteit tussen apathiesyndromen met een verschillende etiologie. Daarom werd geconcludeerd dat het prematuur is om te spreken van "vasculaire apathie", aangezien het gebruik van die term te sterk zou suggereren dat er sprake is van een eigenstandig klinisch syndroom.*

## Methodologische overwegingen en overwegingen voor vervolgonderzoek

Natuurlijk zijn er kanttekeningen te plaatsen bij de bevindingen waarover dit proefschrift rapporteert. Bovendien roepen de resultaten weer nieuwe vragen op en geven daarmee richting aan vervolgonderzoek. Hier wordt in de volgende paragrafen verder op ingaan.

In de eerste drie studies, die gepresenteerd werden in **deel I**, lag de focus op de verbanden tussen cerebrovasculaire ziekte en depressie op oudere leeftijd, zonder dat aandacht besteed werd aan de aan- of afwezigheid van apathie. Achteraf is apathie mogelijk een confounder geweest in deze studies. Bij het plannen van longitudinale etiologische of effectiviteitsstudies op het gebied van depressie op oudere leeftijd, adviseren we onderzoekers ook rekening te houden met apathie en apathiematen af te nemen.

Toen in de studie waarover gerapporteerd werd in **Hoofdstuk 5** extra aandacht besteed werd aan het onderscheid tussen stemmingsproblemen en apathie, leverde dit onverwachte resultaten op. Er kon geen associatie worden aangetoond tussen CSVD en apathie na herstelde depressie, terwijl deze associatie wel in andere populaties was vastgesteld. Verlies van interesse, anhedonie en psychomotore retardatie kunnen zowel symptomen van apathie als van een depressieve stoornis zijn. Daarom werd geopperd dat apathie na herstel van een depressie mogelijk vaker dan tot nu toe werd gedacht restsymptomen van eerdere depressie zouden kunnen zijn. Deze hypothese zou verder onderzoek rechtvaardigen, want depressie komt veel voor, ook op oudere leeftijd, net zoals apathie tijdens en na depressie, en de gevolgen van apathie voor het individuele functioneren en voor de sociale omgeving kunnen ernstig zijn. Sterk zichtbare symptomen van depressie, zoals somberheid, rumineren, pessimisme en suïcidale gedachtes en gedrag, krijgen begrijpelijkerwijs veel aandacht in onderzoek, maar er zou ook voldoende aandacht besteed moeten worden aan apathie en motivatiesymptomen van depressie. Zo zouden in interventiestudies bij depressie ook analyses met apathie als uitkomstmaat verricht kunnen worden, om meer kennis te verwerven over welke behandelingen het risico op apathie na depressie verminderen. Dergelijke studies zouden dan het liefst depressie in een levensloop-perspectief bestuderen, waarbij achteraf gekeken kan worden of er verschillen zijn tussen etiologie, symptomen en prognose van apathie bij depressie op jongere en oudere leeftijd en bij depressie met een vroeg en laat begin.

Dit proefschrift (**Hoofdstuk 3** en **4**) gaat ook over de complexe interacties tussen risicofactoren voor depressie op oudere leeftijd, en de interactie- en plafondeffecten die op kunnen treden als er sprake is van meerdere risicofactoren. Elke risicofactor draagt bij aan het totale risico om depressief te worden. In onderzoek in populaties waarin sprake is van veel risicofactoren en veel depressieve symptomatologie, kan de bijdrage van specifieke risicofactoren in het totale risico lastig te bepalen zijn door interacties en plafondeffecten[46]. Hopelijk is er in de toekomst meer grip op individuele risicofactoren en hun specifieke bijdrage in het ontstaan van depressie door voortschrijdende kennis over statistiek en door big-data analyse. Echter, op dit moment zijn de vaardigheden in het voorspellen van depressie op oudere leeftijd nog beperkt, en zeker nog beperkter als het gaat om het voorspellen van depressie in het individu.

Kennis van de belangrijke risicofactoren voor depressie in specifieke oudere populaties kan ook helpen in het ontwikkelen en implementeren van preventie-onderzoek. Of populaties met een hoog vasculair risico baat zouden hebben bij andere preventiemethoden dan populaties met een hoog risico door een hoog niveau van neuroticisme is onbekend. Meer differentiatie, niet alleen in behandelingen, maar ook op het gebied van preventie zou kunnen bijdragen aan het voorkomen en verminderen van het leed dat depressie veroorzaakt.

En ook als het gaat om apathie, en dan specifiek over het verband tussen CSVD en apathie (**Hoofstuk 6** en **7**), zijn er hiaten in de kennis. Prospectieve studies waarin het voortschrijden van CSVD in relatie tot het ontstaan en beloop van apathie wordt onderzocht, zouden sterk bijdragen aan bewijs voor en inzicht in de causale relatie. Bovendien is het aan te raden dat in interventiestudies bij CSVD naast depressie en cognitie ook apathie als uitkomstmaat wordt meegenomen.

## Overwegingen voor de klinische praktijk

Welke lessen kunnen dokters leren van het onderzoek uit dit proefschrift? De eerste 'take home message' is dat de relatie tussen cerebrovasculaire ziekte en depressie beide kanten op werkt. Clinici wordt geadviseerd om aandacht te besteden aan vasculaire risicofactoren en vasculaire ziekte als er sprake is van een depressie, en om ook aandacht te besteden aan de aanwezigheid van depressieve symptomen bij cerebrovasculaire aandoeningen. De klinische betekenis van deze bevindingen is nog beperkt, omdat de behandeling van vasculaire risicofactoren en vasculaire ziekte bij depressie niet anders is dan gebruikelijk, wat ook geldt voor de behandeling van depressie bij cerebrovasculaire aandoeningen.

Ook bestaat er het risico van tunnel-visie met betrekking tot de oorzaken van een depressie op het moment dat er sprake is van cerebrovasculaire ziekte. Andere risicofactoren, zoals een hoog niveau van neuroticisme, kunnen ook een rol en mogelijk zelfs een grotere rol spelen in het ontstaan of onderhouden van een depressie. Onderzoek modellen voor depressie op oudere leeftijd geven een indicatie van potentiële risicofactoren, maar zijn geen vervanging voor een gedegen klinische beoordeling en analyse van risicofactoren, onderhoudende en beschermende factoren in de individuele patiënt.

Een ander punt van contemplatie voor de arts die patiënten met depressie en apathie behandelt komt voort uit de bevinding dat apathie in herstelde depressie niet significant samenhangt met CSVD (**Hoofdstuk 5**). Deze bevinding onderstreept de overeenkomsten tussen apathie en motivatiesymptomen van depressie en roept de vraag op of en hoe apathie na herstelde depressie samenhangt met de voorafgaande depressie.

We weten nog weinig van de oorzaken en behandeling van apathie na depressie. Wat kunnen we het beste adviseren: antidepressieve of een andere biologische (vervolg) behandeling, psychotherapie of gedragsactivatie (door middel van een gestructureerd dagprogramma)? Op dit moment is er weinig bewijs voor het een of het ander, maar vanwege de serieuze gevolgen van apathie voor het functioneren en de sociale omgeving is het niet verstandig vanuit gebrek aan bewijs niets te doen.

In **Hoofdstuk 6** en **7** werd beschreven er dat in de algemene bevolking en in populaties met neurodegeneratieve aandoening een causaal verband tussen CSVD en apathie werd vastgesteld. Deze informatie kan clinici, patiënten en hun mantelzorgers helpen om de aanwezigheid van apathie bij CSVD te begrijpen en te accepteren. Echter, ook bij apathie in de context van vastgestelde CSVD is er het risico op een tunnelvisie, want apathie kan veel verschillende oorzaken kan hebben en hangt vooral in oudere populaties vaak (ook) samen met depressie en cognitieve achteruitgang. Daarom is het advies voor artsen om een brede analyse te maken van mogelijke risicofactoren en oorzaken van apathie voor elke individuele patiënt, ook als er sprake is van CSVD.

Tot slot, is het belangrijk dat clinici die patiënten zien met depressie op oudere leeftijd en met apathie beseffen dat er nog belangrijke hiaten zijn in onze huidige kennis, met name als het gaat om werkzame behandelingen voor CSVD- of depressie-gerelateerde apathie. Hopelijk motiveert hen dat om samen te werken met onderzoekers door patiënten en hun naasten te informeren over lopende onderzoeken en hen te helpen om deel te nemen aan onderzoek.

## Overwegingen voor het opleiden van de volgende generatie psychiaters:

Voor al diegenen die de volgende generatie psychiaters opleiden onderstreept dit proefschrift opnieuw het belang van epidemiologie in de psychiatrische praktijk. Psychiaters moeten in staat zijn om de waarschijnlijkheid en relevantie van risicofactoren voor depressie op latere leeftijd en voor apathie in verschillende populaties te kunnen inschatten. Ze zouden kennis moeten hebben van CSVD en van hoe CSVD motivatie en initiatief kan beïnvloeden, zodat ze de symptomen die ze bij patiënten zien beter kunnen begrijpen. Ook is het erg belangrijk dat ze leren om deze informatie op een heldere wijze te vertellen aan hun patiënten en hun naasten en/of zorgverleners.

Ook de beperkingen van de huidige ziektemodellen voor depressie op oudere leeftijd en voor apathie zijn belangrijk om te leren, waarin meerdere risicofactoren vaak gezamenlijk voorkomen en elkaar kunnen beïnvloeden. Dat kan de psychiaters van de toekomst helpen om het ziektemodel dat ze opstellen voor de patiënt in hun spreekkamer te zien en te presenteren als een waarschijnlijke verklaring, terwijl ze toch een open mind houden voor alternatieve verklaringen.

Tot slot, benadrukken de resultaten van de studies die in dit proefschrift beschreven zijn het belang van apathie, of motivationele symptomen, in CSVD en in depressie. Psychiaters

wordt aangeraden gedurende de levensloop actief symptomen van apathie uit te vragen bij patiënten en hun naasten of zorgverleners, zeker als er sprake is van CSVD of na herstel van een depressie. En als er sprake is van apathie, om een ziektemodel op te stellen en een gepersonaliseerd behandelvoorstel te doen.

# Referenties


1. Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. *Acta Psychiatr Scand*. 2006;113(5):372-387. doi:10.1111/J.1600-0447.2006.00770.X
2. Meeks TW, Vahia I V., Lavretsky H, Kulkarni G, Jeste D V. A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *J Affect Disord*. 2011;129(1-3):126-142. doi:10.1016/J.JAD.2010.09.015
3. Penninx BWJH, Geerlings SW, Deeg DJH, Van Eijk JTM, Van Tilburg W, Beekman ATF. Minor and major depression and the risk of death in older persons. *Arch Gen Psychiatry*. 1999;56(10):889-895. doi:10.1001/archpsyc.56.10.889
4. Penninx BWJH, Beekman ATF, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001;58(3):221-227. doi:10.1001/ARCHPSYC.58.3.221
5. Wei J, Lu Y, Li K, Goodman M, Xu H. The Associations of Late-life Depression with All-cause and Cardiovascular Mortality: The NHANES 2005-2014. *J Affect Disord*. Published online December 2021. doi:10.1016/J.JAD.2021.12.104
6. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA*. 2011;306(11):1241-1249. doi:10.1001/JAMA.2011.1282
7. Teper E, O'Brien JT. Vascular factors and depression. *Int J Geriatr Psychiatry*. 2008;23(10):993-1000. doi:10.1002/GPS.2020
8. Leung YW, Flora DB, Gravely S, Irvine J, Carney RM, Grace SL. The impact of premorbid and postmorbid depression onset on mortality and cardiac morbidity among patients with coronary heart disease: meta-analysis. *Psychosom Med*. 2012;74(8):786-801. doi:10.1097/PSY.0B013E31826DDBED
9. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis. *Ageing Res Rev*. 2019;50:102-109. doi:10.1016/J.ARR.2019.01.013
10. Rensma SP, van Sloten TT, Launer LJ, Stehouwer CDA. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2018;90:164-173. doi:10.1016/J.NEUBIOREV.2018.04.003
11. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963-974. doi:10.1038/mp.2013.20
12. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report- a critical update. *BMC Med*. 2016;14(1). doi:10.1186/s12916-016-0720-5
13. Culang-Reinlieb ME, Johnert LC, Brickman AM, Steffens DC, Garcon E, Sneed JR. MRI-defined vascular depression: a review of the construct. *Int J Geriatr Psychiatry*. 2011;26(11):1101-1108. doi:10.1002/GPS.2668

14. Grool AM, Van Der Graaf Y, Mali WPTM, Witkamp TD, Vincken KL, Geerlings MI. Location and progression of cerebral small-vessel disease and atrophy, and depressive symptom profiles: the Second Manifestations of ARTerial disease (SMART)-Medea study. *Psychol Med*. 2012;42(2):359-370. doi:10.1017/S0033291711001383

15. Hollocks MJ, Lawrence AJ, Brookes RL, et al. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain*. 2015;138(12):3803-3815. doi:10.1093/brain/awv304

16. Lohner V, Brookes RL, Hollocks MJ, Morris RG, Markus HS. Apathy, but not depression, is associated with executive dysfunction in cerebral small vessel disease. *PLoS One*. 2017;12(5). doi:10.1371/journal.pone.0176943

17. Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry*. 2011;26(2):158-165. doi:10.1002/GPS.2508

18. Groeneweg-Koolhoven I, de Waal M, van der Weele, GM Gussekloo J, van der Mast R. Quality of life in community-dwelling older persons with apathy. *Am J Geriatr Psychiatry*. 2014;22(2):186-194.

19. Burton RL, O'Connell ME, Morgan DG. Cognitive and Neuropsychiatric Correlates of Functional Impairment Across the Continuum of No Cognitive Impairment to Dementia. *Arch Clin Neuropsychol*. 2018;33(7):795-807. doi:10.1093/ARCLIN/ACX112

20. Tsai CF, Hwang WS, Lee JJ, et al. Predictors of caregiver burden in aged caregivers of demented older patients. *BMC Geriatr*. 2021;21(1). doi:10.1186/S12877-021-02007-1

21. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al. Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. *Parkinsonism Relat Disord*. 2015;21(6):629-634. doi:10.1016/J.PARKRELDIS.2015.03.024

22. Eurelings LSM, van Dalen JW, ter Riet G, et al. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data. *Clin Epidemiol*. 2018;10:363-379. doi:10.2147/CLEP.S150915

23. Van Dalen JW, Van Wanrooij LL, Moll Van Charante EP, Brayne C, Van Gool WA, Richard E. Association of Apathy With Risk of Incident Dementia: A Systematic Review and Meta-analysis. *JAMA psychiatry*. 2018;75(10):1012-1021. doi:10.1001/JAMAPSYCHIATRY.2018.1877

24. Robert P, Lanctôt KL, Agüera-Ortiz L, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *Eur Psychiatry*. 2018;54:71-76. doi:10.1016/J.EURPSY.2018.07.008

25. Ligthart SA, Richard E, Fransen NL, et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69(6):636-642. doi:10.1001/archgenpsychiatry.2011.1858

26. Marijnissen RM, Bus BAA, Schoevers RA, et al. Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry*. 2014;22(8):801-810. doi:10.1016/j.jagp.2013.01.001

27. Wouts L, Kessel M van, Beekman ATF, Marijnissen RM, Voshaar RCO. Empirical support for the vascular apathy hypothesis: A structured review. *Int J Geriatr Psychiatry*. 2020;35(1):3-11. doi:10.1002/GPS.5217

28. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22(7):613-626. doi:10.1002/GPS.1723

29. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37(6):1583-1633. doi:10.1161/01.STR.0000223048.70103.F1

30. Schiweck C, Piette D, Berckmans D, Claes S, Vrieze E. Heart rate and high frequency heart rate variability during stress as biomarker for clinical depression. A systematic review. *Psychol Med*. 2019;49(2):200-211. doi:10.1017/S0033291718001988

31. Williams MS, Ziegelstein RC, McCann UD, Gould NF, Ashvetiya T, Vaidya D. Platelet Serotonin Signaling in Patients With Cardiovascular Disease and Comorbid Depression. *Psychosom Med*. 2019;81(4):352-362. doi:10.1097/PSY.0000000000000689

32. Shi S, Liu T, Liang J, Hu D, Yang B. Depression and Risk of Sudden Cardiac Death and Arrhythmias: A Meta-Analysis. *Psychosom Med*. 2017;79(2):153-161. doi:10.1097/PSY.0000000000000382

33. Penninx BWJH. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev*. 2017;74:277-286. doi:10.1016/J.NEUBIOREV.2016.07.003

34. Bevan S, Traylor M, Adib-Samii P, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genomewide associations. *Stroke*. 2012;43(12):3161-3167. doi:10.1161/STROKEAHA.112.665760

35. Zhao F, Yue Y, Jiang H, Yuan Y. Shared genetic risk factors for depression and stroke. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;93:55-70. doi:10.1016/J.PNPBP.2019.03.003

36. Hassell MEC, Piek JJ, Delewi R, et al. Silent cerebral infarcts associated with cardiac disease and procedures. *Nat Rev Cardiol*. 2013;10:696-706. doi:10.1038/nrcardio.2013.162

37. Contrada RJ, Boulifard DA, Idler EL, Krause TJ, Labouvie EW. Course of depressive symptoms in patients undergoing heart surgery: confirmatory analysis of the factor pattern and latent mean structure of the Center for Epidemiologic Studies Depression Scale. *Psychosom Med*. 2006;68(6):922-930. doi:10.1097/01.PSY.0000244391.56598.10

38. Joseph C, Wang L, Wu R, Manning KJ, Steffens DC. Structural brain changes and neuroticism in late-life depression: a neural basis for depression subtypes. *Int psychogeriatrics*. 2021;33(5):515-520. doi:10.1017/S1041610221000284

39. Naarding P, Schoevers RA, Janzing JGE, Jonker C, Koudstaal PJ, Beekman ATF. A study on symptom profiles of late-life depression: the influence of vascular, degenerative and inflammatory risk-indicators. *J Affect Disord*. 2005;88(2):155-162. doi:10.1016/J.JAD.2005.07.002

40. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. *J Gerontol A Biol Sci Med Sci*. 2017;72(3):343-352. doi:10.1093/GERONA/GLW241

41. Carlier A, van Exel E, Dols A, et al. The course of apathy in late-life depression treated with electroconvulsive therapy; a prospective cohort study. *Int J Geriatr Psychiatry*. 2018;33(9):1253-1259. doi:10.1002/gps.4917

42. Oudega ML, Siddiqui A, Wattjes MP, et al. Are Apathy and Depressive Symptoms Related to Vascular White Matter Hyperintensities in Severe Late Life Depression? *J Geriatr Psychiatry Neurol*. 2021;34(1):21-28. doi:10.1177/0891988720901783

43. Lampe IK, Heeren TJ. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *Int psychogeriatrics*. 2004;16(4):481-486. doi:10.1017/S1041610204000766

44. Yuen GS, Gunning FM, Woods E, Klimstra SA, Hoptman MJ, Alexopoulos GS. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *J Affect Disord*. 2014;166:179-186. doi:10.1016/j.jad.2014.05.008

45. Clancy U, Gilmartin D, Jochems ACC, Knox L, Doubal FN, Wardlaw JM. Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis. *The lancet Psychiatry*. 2021;8(3):225-236. doi:10.1016/S2215-0366(20)30431-4

46. Liu Q, Wang L. t-Test and ANOVA for data with ceiling and/or floor effects. *Behav Res Methods*. 2021;53(1):264-277. doi:10.3758/S13428-020-01407-2

# Dankwoord

En dan nu mijn woord van dank voor al degenen die bij hebben gedragen aan dit proefschrift…

Allereerst wil ik Professor Oude Voshaar bedanken. Beste Richard, zonder jou zou ik nooit zo'n vliegende start hebben kunnen maken, zonder jou zou ik geen doorstart hebben kunnen maken en zonder jou had ik het niet af kunnen maken. Het is geweldig hoe jij én als promotor overstijgend nadenkt en richting geeft, én tot in detail meedenkt over de analyses en de tekst.

Daarnaast wil ik mijn tweede promotor, Professor Beekman bedanken. Beste Aartjan, jij hebt direct in het begin van het traject mij op het juiste spoor gezet en toegang gegeven tot de LASA-data. Dat was meteen een prettige samenwerking. Later heb ik het gewaardeerd dat jij filosofie en reflectie het project in blies.

Beste Radboud, mijn copromotor, jou wil ik bedanken voor het stellen van deadlines, voor de juiste opmerking op het juiste moment en voor het bijsturen als er iets spaak dreigde te lopen. Daarmee trok je waar nodig het proces vlot.

Hierbij wil ik ook Professor Buitelaar noemen, die bij de start van dit promotietraject een belangrijke rol had, mij gestimuleerd heeft om onderzoek te doen en een goede opleider voor mij was waar ik veel van geleerd heb. Beste Jan, dank daarvoor.

De manuscriptcommissie bestaande uit Professor Schroevers, Professor van Munster en Professor Verheij wil ik hartelijk danken voor het nauwkeurig lezen van dit proefschrift.

Alle coauteurs wil ik bedanken voor de prettige samenwerking bij het schrijven van de artikelen, waarvan de meeste vrij vlot gepubliceerd werden, maar een enkel artikel wat meer volharding en toewijding vroeg. Hanneke Meulenbroek wil ik bedanken voor haar zorgvuldige en nauwkeurige correcties.

De onderzoeksgroepen van LASA, NBS, NESDO en NESDA wil ik bedanken voor het opzetten en toegankelijk maken van deze cohorten voor onderzoekers. En uiteraard wil ik alle deelnemers aan deze onderzoeken bedanken, zonder wie al dit onderzoek niet mogelijk was en die belangeloos deel hebben genomen aan interviews, tests en bloedafnames.

Pro Persona Research en dan met name Professor Hendriks, Professor Spijker en Professor Thiemens wil ik bedanken voor hun inzet om onderzoek binnen Pro Persona te stimuleren en faciliteren. Graag blijf ik de prettige samenwerking voortzetten.

En nu kom ik dan aan bij mijn naaste collega's van het Expertisecentrum voor ouderenpsychiatrie Maria Mackenzie. Angela, Sharon, Lianne, Patricia, Kees en Anne Lelieveld: bedankt dat jullie altijd én bereid waren waar te nemen waar nodig én geïnteresseerd bleven in mijn toch wel erg lang durende onderzoek…Ook mijn zorgmanager Esther, en programmaleider Anneke, wil ik expliciet bedanken voor de faciliterende houding.

Mijn tweede werkplek is de opleiding psychiatrie en klinische geriatrie van Pro Persona. Hier wil ik allereerst mijn goede vriendin, collega en paranimf Annemarie bedanken voor alles wat we al jarenlang delen en samendoen en voor je prettige, rustige en betrokken houding. Anne Verstraten: we zijn een goede tandem, heel prettig is dat! Ook mijn andere naaste collega's in het opleidingsteam van Pro Persona, en dan noem ik Jolies even met name, wil ik bedanken voor alle belangstelling. En natuurlijk Marja, als secretaresse hart en ziel van de opleiding.

Paul Naarding en Professor Tendolkar. Beste Paul en Indira: het is fijn om met zulke ervaren en wijze collega's samen te werken aan het vormgeven van het regionale onderwijs in de ouderenpsychiatrie.

Ook al mijn andere collega's van Maria Mackenzie, van Pro Persona Nijmegen en van de verpleeghuizen van de Waalboog en ZZG: jullie zijn met te veel om op te noemen maar ik wil jullie bedanken voor af en toe die vraag hoe het er mee stond en dan het geduldig luisteren naar mijn vast te lange antwoord. En hierbij nog een extra woord van dank aan diegenen die hielpen bij de proefpromotie, Annemarie, Froukje, Angela, Esther, Anne en Kim.

En dan zijn daar natuurlijk mijn goede vrienden, die nog veel langer dit traject hebben meegemaakt en geduldig, neutraal en vol vertrouwen zijn gebleven, ook daar waar ik zelf niet meer wist of ik het proefschrift ooit af ging maken. Noor, Anne en Roos, onze tijd samen in Indonesië heeft een band voor het leven gesmeed en ik heb altijd het gevoel bij jullie terecht te kunnen, met jullie te kunnen huilen en lachen. Dank daarvoor. Ook Rosalinde was zo'n goede hechte vriendin. Zij is helaas overleden in 2010 en alleen in gedachten nog bij me, maar toch nog steeds dichtbij. Als ik aan Rosalinde denk zie ik weer die dokter (de enige in Nederland) die destijds haar brieven ondertekende met een handgeschreven 'Rosalinde' met niet alleen een gezichtje in de 'O', maar ook nog een zwaaiend handje eraan vast gekriebeld. Altijd jezelf blijven, altijd ruimte voelen om te mogen voelen, lachen en spelen. Bedankt.

Ook mijn boekenclubvriendinnen zijn belangrijk voor me. Wyke, Nienke, Marloes de Jong, Noor (opnieuw) en Monique: jullie zijn mijn klankboord en waar nodig mijn geweten. Wat een slimme, geëngageerde dames bij elkaar. Jullie hebben natuurlijk altijd gelijk maar soms verzet ik er me nog even tegen!

En mijn dierbare vriendin Marloes Keulemans-Kuipers heeft me tijdens wandelingen en etentjes jarenlang aangehoord en gesteund met haar nuchterheid en warmte.

Wat een rijkdom, zoveel vriendinnen, en dan heb ik mijn Brakwakvrienden nog niet eens genoemd, hierbij dan.

Daarbij komen dan ook nog eens twee warme Brabantse families, mijn twee vangnetten. Ik zal beginnen met de familie Grootens. Jannie en Peter, geweldig hoe jullie al die jaren er altijd voor ons en onze kinderen waren en zelfs bereid waren in ons huis, het door mij gemaakte oppas-draaiboek af te draaien, boordevol taxiritjes en huishoudelijke instructies, zodat Koen en ik naar een congres konden of konden gaan wandelen.

Mijn eigen familie, de familie Wouts, wil ik ook graag bedanken. Met name mijn zus Froukje, omdat ze mijn paranimf wilde zijn. En natuurlijk mijn ouders, Helma en Wil, bedankt voor het basisvertrouwen dat ik heb gekregen door op te groeien in jullie warme, open en gezellige gezin. En ook bedankt voor al het oppassen en alle wijze adviezen en praktische steun. Waarbij mijn moeder Helma niet alleen het schilderij heeft gemaakt dat in mijn spreekkamer hangt, maar ook het prachtige beeld dat mijn proefschrift zo opfleurt en opsiert.

Mijn lieve kinderen Saar, Jonas en Annika wil ik bedanken dat jullie mij behoeden voor het worden van een echte workaholic omdat het daarvoor nu eenmaal te gezellig is thuis met jullie. Het is een voorrecht jullie te zien opgroeien, alle drie anders, alle drie eigen.

Lieve Koen, jou wil ik bedanken voor je scherpe inzichten, voor je vertrouwen in mij en mijn capaciteiten, maar vooral voor je liefde.

# Curriculum Vitae

Lonneke Wouts was born on 24 June 1977 in Tilburg, the Netherlands. After completing secondary education (Gymnasium, Cum Laude) at the st. Odulphus Lyceum in Tilburg in 1995, she started her Bachelor Medicine at the University of Utrecht. During Medical School she was a student-assistant for several courses (basic and advanced neurology, basic and advanced communication skills. In 1998, she worked for several months on the island of Batam, Indonesia, for a research project on the prevention and prevalence of Hepatitis.

After her graduation and registration as a physician in 2003, she started working at the Geriatrics department of Hospital Gooi-Noord in Blaricum. Later that year, she switched to working as a physician at the department of Old Age Psychiatry of Mental Health Institute Altrecht in Utrecht. In 2004 she started as a psychiatrist-in-training at the Radboud University Medical Centre in Nijmegen. During this time, she worked at the Radboud University Medical Centre, CWZ General Hospital (Nijmegen) and Mental Health Institute Pro Persona (Nijmegen). As a psychiatrist-in-training she was a member of the Dutch association of psychiatrists-in-training (SAP) and of the committee for the assessment of psychiatry training-institutions (opleidingsvisitatiecommissie). Also, she started research into *vascular risk factors for depression* as a PhD student.

She started her career as an Old-Age psychiatrist (2009) at the Old-Age department of GGZ Oost-Brabant/GGZ Land van Cuijk in Boxmeer, combining clinical work with the PhD project. In 2012 she switched to the Old-Age psychiatry department of Pro Persona in Nijmegen. In 2018 the research topic of the PhD project was widened according to developing knowledge and insights to *vascular risk factors for depression and apathy.*

She followed advanced courses in management for psychiatrists, ethics for health care professionals and law for psychiatrists. From 2017-2019 she was acting medical director (waarnemend geneesheer-directeur) of Pro Persona Nijmegen. Since 2019 she has been working as a trainer and head of the Old-Age Psychiatry residency program of Pro Persona.

At present, she still works as a clinician, researcher and trainer of Old-Age Psychiatry.