White matters

The influence of cerebral small-vessel disease on depression, cognition and functioning

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Witte Stof

De invloed van microvasculaire schade in de hersenen op depressie, cognitie en functioneren

(met een samenvatting in het Nederlands)

Proefschrift

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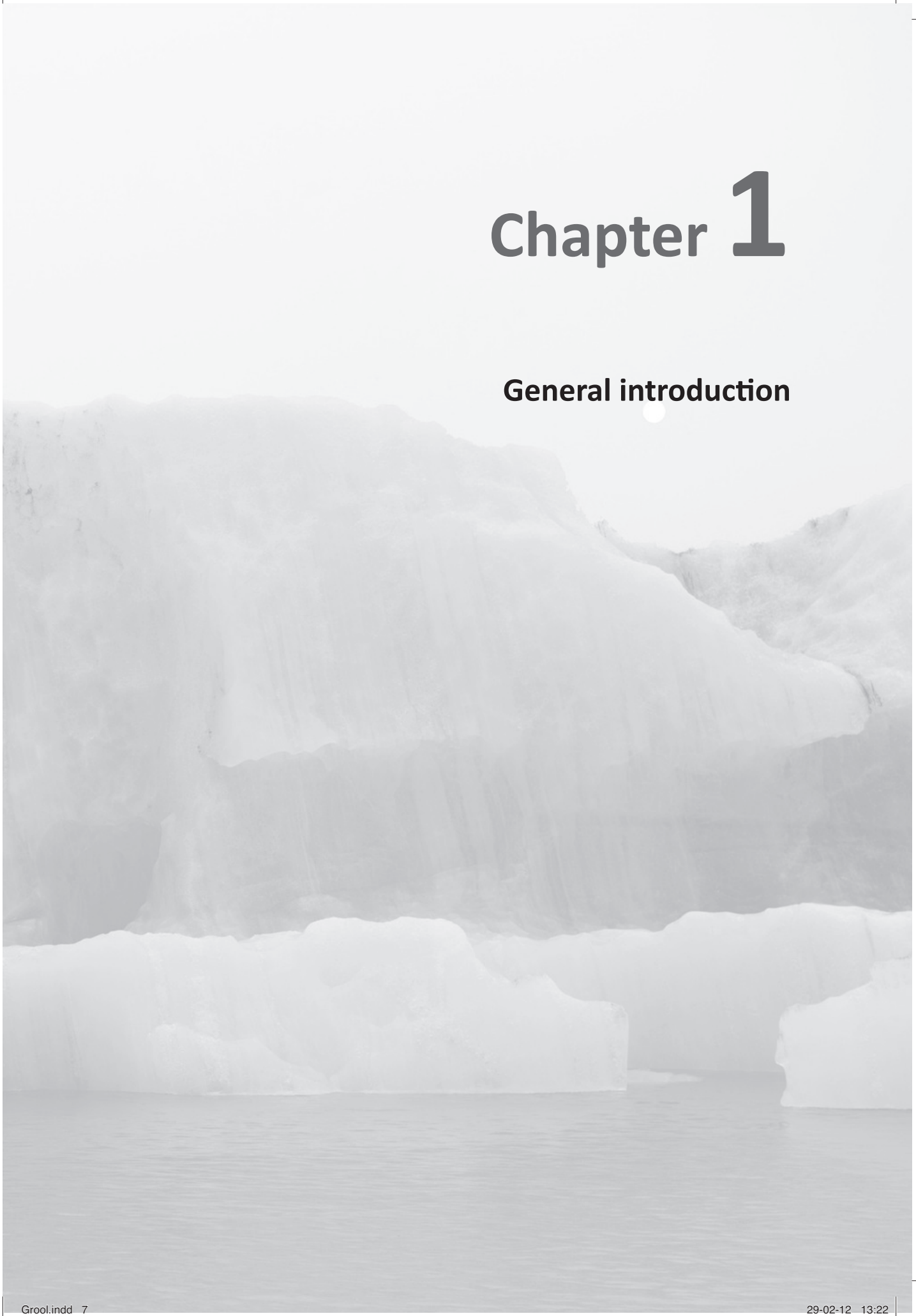
Chapter 1

General introduction



General introduction

Ischemic heart disease and stroke are leading causes of death worldwide, and among the top contributors to global burden of disease [1]. In western countries, cardiovascular disease accounts for 1 of every 3 deaths, with 20% of cardiovascular deaths occurring in persons <65 years of age [2]. Moreover, during the lifespan cardiovascular disease is associated with substantial impairments in self-rated functioning [3,4] and an increased risk of cognitive decline [5,6] and late-life depression [7,8]. Various pathophysiological factors have been investigated as possible mechanisms by which cardiovascular disease may be associated with worse self-rated functioning, cognition, and late-life depression, such as cardiovascular risk factors, dietary and lifestyle patterns, genetic predisposition, inflammatory processes, hyperactivity of the hypothalamic-pituitary-adrenocortical axis and lower heart-rate variability [9]. Despite these efforts, it remains uncertain which of these factors, if any, can explain the observed associations of cardiovascular disease with worse self-rated functioning, cognition, and late-life depression [10].

An alternative mechanism that may explain the relation between cardiovascular disease and worse self-rated functioning, cognition, and late-life depression is the presence of structural brain changes, characterized by cerebral small-vessel disease and atrophy. Cerebral small-vessel disease and atrophy are both strongly related to common vascular risk factors [11], and are frequently observed on brain magnetic resonance imaging (MRI) in patients with atherosclerotic disease [12]. Increasing evidence suggests that the different clinical manifestations of cerebral small-vessel disease and atrophy depend not only on lesion severity, but also on the strategic location in specific brain regions involved in regulation of emotions and physical and cognitive functions.

The relation between cerebral small-vessel disease and depression in particular has received much interest. The 'vascular depression' hypothesis proposed that impaired neural connectivity resulting from disruption of frontal-subcortical networks may be a mechanism by which cerebral small-vessel disease predisposes, precipitates or perpetuates depression in late life [13,14]. Because frontal-subcortical networks are primarily involved in the regulation of motivational behaviour [15,16], 'vascular depression' is thought to be characterized by the presence of primarily motivational symptoms [17]. Although various studies observed a relationship between cerebral small-vessel disease and the presence of clinically relevant depressive symptoms [18-21], the direction of causation remains a topic of debate [22-24]. So far, longitudinal studies yielded inconclusive findings as to whether cerebral small-vessel disease is a cause of depression, a consequence, or whether both may result from a mutual underlying mechanism. In addition, direct evidence that the presence of cerebral small-vessel disease in frontal-subcortical brain regions is associated with a characteristic

motivational profile of depression is scarce [25,26], and recent results even suggest that these motivational symptoms may be expressions of small-vessel-related apathy rather than depression characteristics [27,28].

Thesis objectives

The aim of this thesis was first to investigate the influence of cerebral small-vessel disease and atrophy on self-rated functioning, depressive symptoms, cognitive performance and mortality. In addition, we examined to which extent the observed associations depended on the strategic location of structural cerebral changes in different brain regions. To improve our understanding on the direction of causation, we also investigated the bidirectional relation between cerebral small-vessel disease, self-rated functioning and depressive symptoms. We not only examined whether cerebral small-vessel disease may be a risk factor for lower self-rated functioning, depressive symptoms and mortality, but also examined the relation in the opposite direction by investigating whether depressed mood is a risk factor for progression of cerebral small-vessel disease.

Study populations

Data from two large cohort studies were used; the Second Manifestations of ARTerial disease (SMART) study and the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study.

The SMART study is an ongoing prospective cohort study in patients newly referred to the University Medical Center Utrecht with symptomatic atherosclerotic disease or risk factors for atherosclerosis [29], and is aimed at investigating the prevalence of concomitant arterial disease at other sites and studying the incidence of future cardiovascular events and its predictors in patients at high vascular risk. Between 2001 and 2005, patients with symptomatic atherosclerotic disease received MRI of the brain in addition to standard vascular screening as part of the SMART-MR study [30]. Follow-up measurements took place between 2006 and 2009, and an ancillary study, SMART-Medea (Memory, depression and aging), was started to investigate brain changes associated with psychosocial vulnerability and stress factors [31]. For this thesis, data were used from the SMART study, the SMART-MR study and the SMART-Medea study.

The AGES-Reykjavik Study is an ancillary study to the Reykjavik Study, a prospective population-based cohort study of older persons intended to investigate the contribution of genetic susceptibility, environmental factors, and gene-environment interaction to clinical and subclinical disease [32]. Between 2002 and 2006, a random sample of survivors from the Reykjavik study underwent clinical examinations, questionnaires, blood samples, cognitive testing and brain MRI as part of the AGES-Reykjavik Study. For this thesis, data were used from 4354 participants without dementia in the AGES-Reykjavik Study.

Outline

In chapter 2 we investigated the relation between cerebral small-vessel disease, self-rated functioning and the risk of adverse events in patients with arterial disease. In chapter 2.1 we examined progression of WML volume in relation to changes in self-rated physical and mental functioning during 4 years follow-up. In chapter 2.2 the influence of self-rated physical and mental functioning on the risk of future vascular events and mortality is examined. Chapter 2.3 describes the combined effect of cerebral small-vessel disease and mood problems on the risk of mortality. In chapter 3.1 we investigated whether depressed mood is associated with an increased progression of WML volume, and also examined the relative contribution of antidepressant use and mood symptoms to this association. In chapter 4 we investigated the influence of cerebrovascular disease and atrophy in different brain regions on depressive symptoms and cognitive performance. We investigated different structural MRI correlates of depressive symptoms and cognitive functioning in chapter 4.1. In chapter 4.2 we commented on an article on the location of WML and vascular risk factors in relation to late-life depression. In chapter 5 we examined the relation between the location of cerebral small-vessel disease in different brain regions and depressive symptom characteristics. In chapter 5.1 we assessed the depressive symptom characteristics associated with the progression and location of cerebral small-vessel disease and atrophy in different brain regions. In chapter 5.2 we investigated the influence of cerebral small-vessel disease in different brain regions on the course of depressive symptom profiles during three years follow-up. In chapter 6.1 we investigated whether the symptoms associated with cerebral small-vessel disease and atrophy may be more indicative of apathy or depression. Based on our results we will discuss in chapter 7 whether the 'vascular depression' hypothesis holds true, and the findings of all different studies in this thesis are summarized in chapter 8.

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Chapter 2

Cerebral small-vessel disease, self-rated health status and clinical prognosis

Chapter 2.1

Progression of white matter lesion volume and health-related quality of life in patients with symptomatic atherosclerotic disease. The SMART-MR study

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Abstract

Objectives

Mechanisms influencing the course of physical and mental functioning after an atherosclerotic event are unclear. We examined effects of white matter lesion (WML) activity on changes in functioning in patients with symptomatic atherosclerotic disease.

Methods

In 486 patients (58±9 years) of the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, volumetric WML measurements on 1.5T MRI were performed at baseline and 3.9±0.4 years follow-up. Functioning was assessed with the modified Short-Form 12 (SF-12) questionnaire. Associations of WML progression with changes in functioning were adjusted for age, sex and vascular risk factors.

Results

Physical functioning (baseline: 44, 10^{th}-90^{th} percentile 29-55) improved, whereas mental functioning (baseline: 51, 10^{th}-90^{th} percentile 32-60) declined during follow-up. WML progression (highest quartile versus rest) contributed to a stronger decline in mental functioning (B=-1.76, 95% CI -3.11 to -0.42), but did not influence changes in physical functioning.

Conclusions

Progression of WML volume contributes to a decline in mental functioning in patients with symptomatic atherosclerotic disease.

Introduction

Ischemic heart disease and stroke are leading causes of disability and mortality worldwide [1]. As a result of improved survival and the lifelong aspect of these diseases, health-related quality of life (HRQoL), including physical and mental functioning, has become an increasingly important clinical and research outcome when evaluating burden of disease and treatment benefits. In addition, reduced physical and mental functioning do not only interfere with daily living, they also increase the risk of incident ischemic vascular events and mortality [2-4]. Compared to the general population, HRQoL is substantially lower in patients with ischemic heart disease and stroke, especially in the domain of physical functioning [5-7]. A recent study indicated that HRQoL is not only lower in the acute phase of recovery from stroke, but can decline up to five years post-stroke in survivors free from recurrence of stroke or a myocardial infarction [8]. Also, marked impairments in HRQoL have been observed in patients with other manifestations of atherosclerotic disease, including peripheral arterial disease [9,10] and abdominal aortic aneurysm [11,12].

Patients with symptomatic vascular disease frequently have atherosclerotic changes in the small vasculature in the brain, which are characterized by white matter lesions (WML) on magnetic resonance imaging (MRI) [13]. Although WML are often asymptomatic, they have been identified as a risk factor for functional decline [14], late-life depression [15,16] and cognitive impairment [17-19]. It has been suggested that greater disease activity, characterized by an accelerated progression of WML volume, is an important underlying mechanism contributing to this elevated risk [20,21], but longitudinal studies are still relatively scarce. Whether greater progression of WML volume is also associated with a poorer HRQoL has not been studied yet, although it could be expected that more subtle impairments in physical and mental functioning could already be present in patients with greater WML disease activity, before the development of depression or functional decline. In addition, it is unknown whether the influence of WML progression on physical and mental functioning is comparable between patients with different locations of symptomatic atherosclerotic disease.

Our first aim was to investigate the course of physical and mental functioning in patients with different manifestations of atherosclerotic disease over four years of follow-up. Second, we examined whether greater progression of WML volume contributed to poorer physical and mental functioning in these patients, and whether these associations depended on the location of symptomatic atherosclerotic disease.

Materials and methods

Participants

Data were used from the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study aimed to investigate brain changes on MRI in 1309 independently living patients with symptomatic atherosclerotic disease. Details of the design and participants have been described elsewhere [13]. For the current study, data were used from 989 patients newly referred to the University Medical Center Utrecht between January 2002 and December 2005 with manifest peripheral arterial disease, coronary artery disease, cerebrovascular disease or abdominal aortic aneurysm without MR contraindications and available data on the HRQoL questionnaire. During a 1-day visit to our medical center, an MRI of the brain, physical examination, blood and urine sampling were performed. Risk factors, medical history, and functioning were assessed with questionnaires.

Between January 2006 and May 2009, all participants still alive were invited for follow-up measurements, including MRI of the brain, neuropsychological testing, a physical examination, blood and urine sampling, risk factors, medical history, and functioning. The SMART-MR study was approved by the ethics committee of our institution and written informed consent was obtained from all participants. In total, 585 of the surviving cohort (62% of n=943) gave written informed consent; 346 (37%) persons refused, and 12 (1%) were lost to follow-up.

Magnetic resonance imaging protocol

MR investigations were performed on a 1.5-Tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE): 235/2 ms; flip angle, 80º), a transversal T2-weighted turbo spin-echo sequence (TR/TE: 2200/11 ms and 2200/100 ms; turbo factor 12), a transversal T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI): 6000/100/2000 ms) and a transversal inversion recovery (IR) sequence (TR/TE/TI: 2900/22/410 ms) (field of view 230x230 mm; matrix size, 180x256; slice thickness, 4.0 mm; no gap; 38 slices).

Brain segmentation

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique has been described elsewhere [22,23]. The segmentation program distinguishes cortical gray matter, white matter, sulcal and ventricular cerebrospinal fluid (CSF), and lesions. The results of the segmentation analysis were visually checked for the presence of infarcts and adapted if necessary to make a distinction between WML and infarct volumes. Total brain volume was calculated

by summing the volumes of gray and white matter and, if present, the volumes of WML and infarcts. All volumes cranial to the foramen magnum were included. As a result, the total brain volume includes the cerebrum, brainstem and cerebellum. Total intracranial volume (ICV) was calculated by summing the total brain volume and the volumes of the sulcal and ventricular CSF.

Infarcts and white matter lesions

The whole brain was visually searched for infarcts by a trained investigator and a neuroradiologist. Raters were blinded to history and diagnosis of the patient. Discrepancies in rating were re-evaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images in order to distinguish them from WML. Dilated perivascular spaces were distinguished from infarcts on the basis of their location, form, and the absence of gliosis. The location, affected flow territory and type were scored for every infarct. WML volumes obtained with the segmentation program were summed to obtain total WML volume. Volumes of WML were normalized for ICV, and expressed as percentage of ICV.

Physical and mental functioning

At baseline and follow-up, patients completed the Short Form-12 (SF-12) [24], a shortened version of the Short Form-36 (SF-36) Medical Outcomes Study Health Survey [25] to measure HRQoL at baseline and follow-up. The SF-12 questionnaire includes 1 or 2 items from each of the 8 health summary scales of the SF-36 [26], and enables calculation of the Physical (PCS) and Mental Component Summary scales (MCS). The SF-12 summary scales are positively scored and normalized to a general population mean of 50 with standard deviation of 10. Higher SF-12 scores indicate better HRQoL; a positive change in SF-12 scores indicates an improvement, and a negative change a deterioration in HRQoL. Because of its brevity, the SF-12 is considered advantageous to the SF-36 for large studies focusing on overall physical and mental functioning [26].

Severity of atherosclerotic disease at baseline

In patients with peripheral arterial disease, severity of vascular disease at baseline was assessed using the Fontaine scale [27]. Stage 1 (pain-free walking distance >200 m) and stage 2 (pain-free walking distance <200 m) were defined as mild or moderate ischaemia, whereas stage 3 (rest pain) and stage 4 (ulceration or gangrene) were defined as severe ischaemia. In patients with coronary artery disease, disease severity was rated according to the number of coronary arteries with marked atherosclerosis (>70% stenosis or fractional flow reserve <0.80 or treatment of the vessel). One-vessel, two-vessel, three-vessel, left main disease

with or without right coronary artery involvement was rated in all coronary artery disease patients on the basis of coronary angiography reports. Information was incomplete in some patients, and additional information was obtained from percutaneous coronary intervention or coronary artery bypass grafting reports. For patients with cerebrovascular disease, disease severity was classified with a handicap scale, the modified Rankin Scale (mRS) [28].

Other variables

During the visit to the medical center, an overnight fasting venous blood sample was taken to determine glucose levels. Systolic and diastolic blood pressures (mm Hg) were measured twice with a sphygmomanometer and averaged. Hypertension was defined as mean systolic blood pressure ≥160 mm Hg, mean diastolic blood pressure ≥95 mm Hg or self reported antihypertensive drug use. Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/L or self reported use of oral antidiabetic drugs or insulin. Smoking habits and alcohol intake were assessed with questionnaires. Pack-years of smoking was calculated, and alcohol use was categorized into never, past, and current.

Study sample

Of the 585 patients participating at follow-up, data on baseline or follow-up MRI variables were missing in 74 patients (no MR (n=41), irretrievable MR data (n=5), missing FLAIR images (n=7), or artefacts (n=21)). Of these, HRQoL data at follow-up were missing in 17 patients. Of these 494 patients, data on vascular risk factors were missing in 8 patients. This resulted in a total study sample of 486 patients.

Compared to patients who were lost to follow-up (n=503), patients who participated at follow-up (n=486) were significantly younger (mean 57.5 versus 59.6 years) at baseline, had less often hypertension (50% versus 57%) and diabetes mellitus (16% versus 25%), more often reported current alcohol intake (79% versus 72%), had lower WML volume (median 1.3 versus 1.7 mL), had better mental functioning (median 51.0 versus 48.3), and were less often included with peripheral arterial disease (19% versus 26%) or abdominal aortic aneurysm (5% versus 11%) (table 1).

Data analysis

First, we calculated changes in physical and mental functioning after on average 4 years of follow-up in the total sample, and then compared changes in physical and mental functioning between different locations of symptomatic atherosclerotic disease using generalized linear models with physical and mental functioning scores at follow-up as the dependent variables and location of symptomatic atherosclerotic disease, age, sex, baseline physical or mental functioning and follow-up time as independent variables.

Table 1 Baseline characteristics of patients with complete data and of those lost to follow-up

	Complete data at follow-up (n=486)	Lost to follow-up (n=503)
Age[¥] (years)	58 ± 9.3	60 ± 10.2
Male gender (%)	80	79
Diagnosis of symptomatic atherosclerotic disease[‡]		
- Peripheral arterial disease	19	26
- Coronary artery disease	65	61
- Cerebrovascular disease	24	23
- Abdominal aortic aneurysm	5	11
Severe atherosclerotic disease[£]	11	9
Smoking[†] (pack-years)	21 (0-53)	18 (0-50)
Alcohol use		
- Never	13	18
- Former	7	11
- Current	79	72
Hypertension (%)	50	57
Diabetes mellitus (%)	16	25
Total intracranial volume[¥] (mL)	1467 ± 127	1457 ± 132
Absolute total WML volume[†] (mL)	1.3 (0.4-5.8)	1.7 (0.6-8.3)
Physical functioning[†]	44 (29-55)	43 (26-54)
Mental functioning[†]	51 (32-60)	48 (29-60)

WML, White matter lesions; mRS, Modified Rankin Scale

[‡] The different groups of symptomatic atherosclerotic disease do not add up to the total study sample of 486, because various locations of symptomatic atherosclerotic disease can occur within one patient.

[£] Defined as patients with coronary artery disease and three-vessel or left main disease at inclusion, patients with cerebrovascular disease and a mRS grade ≥2 at inclusion, or patients with peripheral arterial disease with Fontaine grade ≥3 at inclusion.

[¥] Mean ± SD

[†] Median, (10^{th}-90^{th} percentile)

Second, linear regression analysis was used to investigate whether greater progression of WML volume was associated with changes in physical and mental functioning. Progression of WML volume was defined as the difference in WML volume (% of ICV) between baseline and follow-up. We divided WML progression into quartiles, and dichotomized WML progression (highest quartile (n=126) versus three lowest quartiles (n=360)) to investigate whether patients with greatest progression showed a different course of physical and mental functioning than patients with no or minimal WML progression. Analyses were first performed in the total sample, and because we expected that associations could be

influenced by the type of underlying atherosclerotic disease, we repeated the analyses within strata of locations of atherosclerotic disease. In model I, associations were adjusted for age, sex, baseline physical or mental functioning and follow-up time. We additionally adjusted for smoking, alcohol use, hypertension and diabetes mellitus in model II, because it is not clear to what extent these vascular risk factors are confounders or preceding factors in the pathway between WML volume and functioning, or both.

We repeated the analyses after excluding patients with severe atherosclerotic disease at baseline, defined as patients with coronary artery disease and three-vessel or left main disease at inclusion, patients with cerebrovascular disease and a mRS grade ≥2 at inclusion, or patients with peripheral arterial disease with Fontaine grade ≥3 at inclusion. This was done to assess to what extent the observed associations between small-vessel disease and functioning were influenced by the severity of macrovascular disease.

Further, to examine whether associations were independent of incident vascular events during follow-up, analyses were repeated after excluding patients who experienced a new vascular complication (non-fatal ischemic stroke or myocardial infarction) between baseline and follow-up. In all analyses, 95% confidence intervals are given. SPSS version 15.0 (Chicago, Ill, USA) was used to analyze our data.

Results

Baseline characteristics are summarized in table 2. Mean age of the study population was 58±9 years and 80% was male. At baseline, median physical functioning was 44 (10-90th percentile 29-55) and mental functioning was 51 (10-90th percentile 32-60).

Mean elapsed time between the vascular event and screening date was 2.1±1.4 months. In the total sample, physical functioning improved (median 3.8, 10th-90th percentile -6.5 to 18.3), and mental functioning deteriorated (median -4.0, 10th-90th percentile -14.0 to 13.0) after a mean follow-up of 3.9±0.4 years. When different locations of atherosclerotic disease were identified, physical functioning improved in all groups (figure 1). This improvement was significantly lower in patients with cerebrovascular disease compared to patients with other locations of symptomatic atherosclerotic disease (B=-2.58, 95% CI -4.29 to -0.87). Mental functioning deteriorated in all groups, without any significant differences between different locations of symptomatic atherosclerotic disease (figure 1).

Table 2 Baseline characteristics

	Total sample (n=486)	Peripheral arterial disease (n=90)‡	Coronary artery disease (n=318)‡	Cerebrovascular disease (n=115)‡	Abdominal aortic aneurysm (n=26)‡
Age¥ (years)	58 ± 9.3	56 ± 10.2	58 ± 9.0	59 ± 9.9	62 ± 7.9
Male gender (%)	80	66	86	76	96
Smoking† (pack-years)	21 (0-53)	26 (1-56)	18 (0-51)	22 (0-53)	32 (7-76)
Alcohol use					
- Never	13	16	12	15	8
- Former	7	10	8	4	4
- Current	79	74	80	82	89
Hypertension (%)	50	58	47	61	54
Diabetes mellitus (%)	16	17	16	18	27
ICV¥ (mL)	1467 ± 127	1437 ± 132	1474 ± 123	1467 ± 128	1507 ± 125
WML volume† (mL)	1.3 (0.4-5.8)	1.4 (0.5-4.6)	1.3 (0.3-4.7)	2.2 (0.4-11.2)	1.8 (0.5-10.3)
Physical functioning†	44 (29-55)	40 (20-53)	44 (31-55)	46 (31-56)	43 (32-55)
Mental functioning†	51 (32-60)	50 (33-60)	51 (31-60)	51 (34-59)	52 (34-58)

ICV, Intracranial volume; WML, White matter lesion

‡ The different groups of symptomatic atherosclerotic disease do not add up to the total study sample of 486, because various locations of symptomatic atherosclerotic disease can occur within one patient.

¥ Mean ± SD

† Median, (10th-90th percentile)

Progression of WML volume

Patients with greatest progression of WML volume (highest quartile, >0.07% increase in WML volume as % of ICV) showed a significantly stronger deterioration in mental functioning than patients with lower WML progression (B=-1.76, 95% CI -3.11 to -0.42; figure 2) in model I. Additional adjustment for vascular risk factors did not change the results (data not shown). When analyses were repeated within different strata of locations of symptomatic atherosclerotic disease, greater WML progression was associated with a stronger deterioration in mental functioning in all patients except for patients with cerebrovascular disease (figure 3), although the deterioration was statistically significant only in patients with coronary artery disease (model I, B=-2.03, 95% CI -3.61 to -0.45). Additional adjustment for vascular risk factors did not change these associations.

Greater progression of WML volume was not significantly associated with changes in physical functioning at follow-up in model I in the total sample (B=-0.04, 95% CI -1.79 to 1.72; figure 2), or within strata of patients with coronary artery disease (B=0.02, 95% CI -2.26 to 2.30), peripheral arterial disease (B=1.26, 95% CI -3.65 to 6.16), cerebrovascular disease (B=0.00, 95% CI -3.46 to 3.46) or abdominal aortic aneurysm (B=-0.38, 95% CI -7.07 to 6.32).

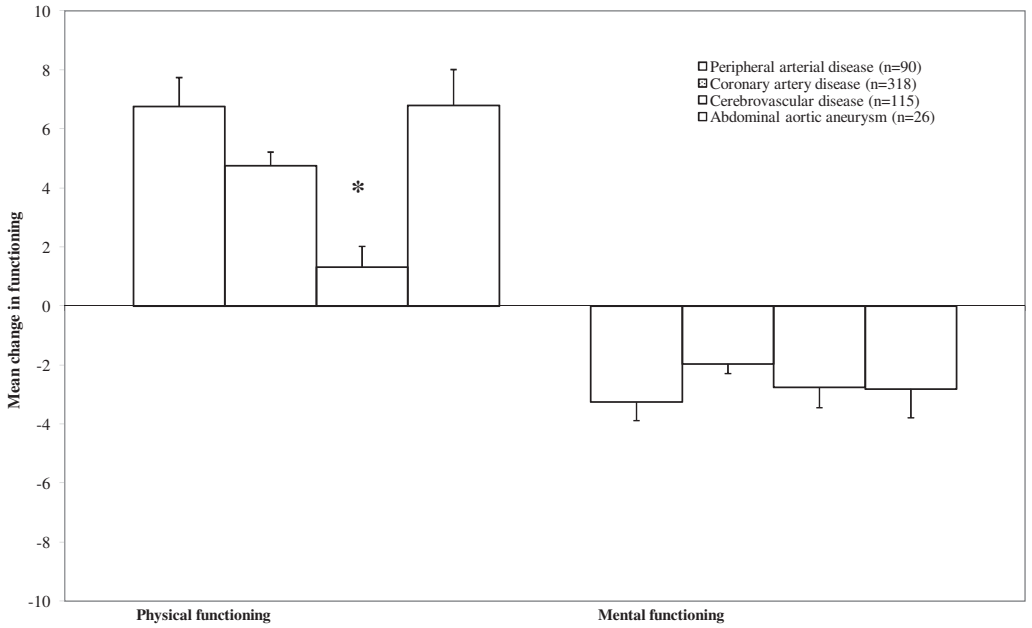

Figure 1 Mean changes in physical and mental functioning for different locations of symptomatic atherosclerotic disease, adjusted for age, sex, baseline functioning and follow-up time. Significant differences, compared to other locations of symptomatic atherosclerotic disease, are indicated with an asterix.

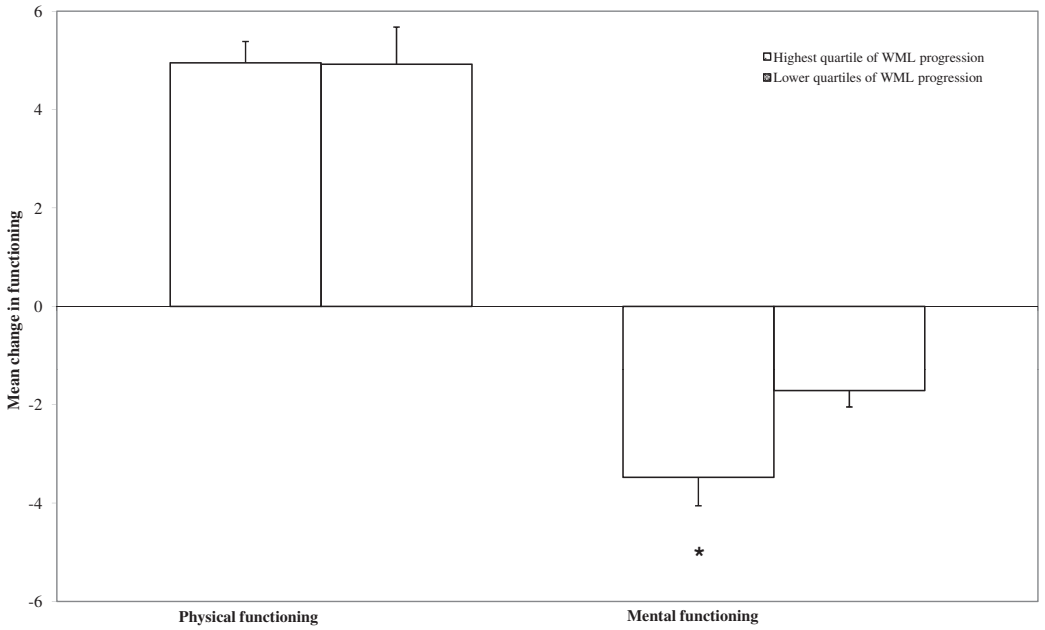

Figure 2 Mean changes in physical and mental functioning for patients with greatest progression of white matter lesion (WML) volume (highest quartile, >0.07% increase in WML volume as % of ICV) versus patients in the three lowest quartiles of progression, adjusted for age, sex, baseline functioning and follow-up time. Significant differences are indicated with an asterix.

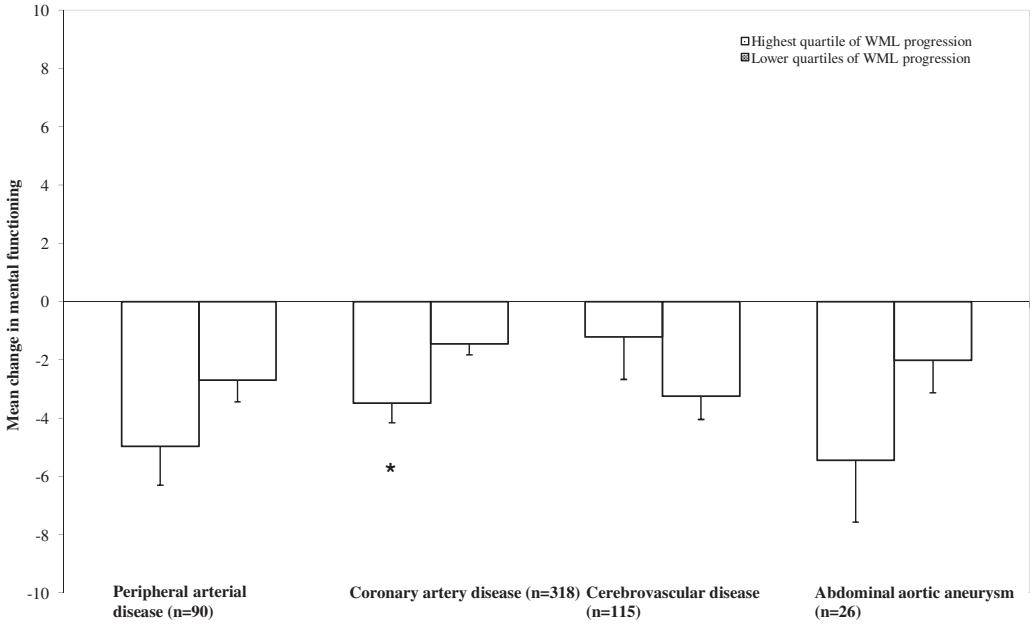

Figure 3 Mean changes in mental functioning for patients with greatest progression of white matter lesion (WML) volume versus patients in the three lowest quartiles of progression, for different locations of symptomatic atherosclerotic disease, adjusted for age, sex, baseline functioning and follow-up time. Significant differences are indicated with an asterix.

Excluding patients with most severe symptomatic atherosclerotic disease (n=46) did not materially change the results. Greater WML progression was still significantly associated with a stronger deterioration in mental functioning (model I, B=-1.82, 95% -3.25 to -0.38).

Between baseline and follow-up, 17 patients experienced a non-fatal vascular event. Excluding these patients did not change the observed associations of greater WML progression with a stronger deterioration in mental functioning (model I, B=-1.83, 95% CI -3.20 to -0.46).

Discussion

In a cohort of patients with different manifestations of symptomatic atherosclerotic disease, physical functioning substantially improved in all patients after four years of follow-up, although the improvement was less in patients with cerebrovascular disease. Mental functioning declined in all types of symptomatic atherosclerotic disease. Greater progression of WML volume over four years of follow-up was associated with a stronger decline in mental functioning in all patients except for those with cerebrovascular disease.

To our knowledge, this is the first study directly investigating the influence of WML progression on the course of physical and mental functioning in patients with different manifestations of symptomatic atherosclerotic disease. A strength of this study is that by including patients with different locations of symptomatic atherosclerotic disease we could investigate whether the effect of WML progression on physical and mental functioning depended on the type of underlying vascular disease. Furthermore, volumetric WML assessment provided estimates that are more precise and less influenced by observer-bias than visual rating scales [29-31], and enabled the measurement of relatively small volume changes over time. In addition, we included a large number of patients, and the extensive information available on cardiovascular risk factors and the extent of clinical and subclinical atherosclerosis made it possible to adjust for potential confounders.

A limitation of this study is that despite the large sample size, relatively few patients had peripheral arterial disease, cerebrovascular disease or abdominal aortic aneurysm. Although similar associations were found in patients with coronary artery disease, peripheral arterial disease and abdominal aortic aneurysm, the relatively low number of patients with locations of symptomatic atherosclerotic disease other than coronary artery disease contributed to large confidence intervals and possibly non significant relations in these patients. Further, the largest impact on physical and mental functioning would be expected in patients suffering most severe atherosclerotic events. Because these patients are less likely to participate in our study, this could have contributed to a relative underestimation of the effect. Moreover, patients who participated at follow-up were healthier at baseline, with fewer vascular risk factors, lower WML volume and higher mental functioning than patients lost to follow-up. Therefore, the changes in physical and mental functioning might have been less prominent in the total cohort. Also, because baseline mental functioning was higher in patients with complete data at follow-up, regression to the mean could have contributed to the observed decline in mental functioning after four years. On the other hand, the selection of relatively healthy patients could have resulted in a decreased contrast between those with greatest WML progression and those without, which could have led to an underestimation of the effect of WML progression on changes in mental functioning.

In recent years, HRQoL has become an increasingly important clinical and research outcome measure when evaluating burden of disease and treatment benefits in patients with atherosclerotic disease. Population-based studies have shown that patients with various manifestations of symptomatic atherosclerotic disease have a poorer HRQoL compared to the general population, with most pronounced effects on physical functioning [5-7,9,10]. It is unclear whether physical and mental functioning return to population-levels after the acute phase of recovery, or whether functioning remains lower, or perhaps even further declines after the initial event.

Our data showed that physical functioning was substantially lower in patients with symptomatic atherosclerotic disease in the acute phase of recovery from an atherosclerotic event compared to previously published age-adjusted population norms [32]. In a previous population-based study, a prolonged decline in HRQoL was observed in stroke survivors free from recurrent stroke or myocardial infarction [8]. Although we found an improvement in physical functioning in our sample of patients with cerebrovascular disease after four years follow-up, this improvement was substantially lower compared to patients with other locations of symptomatic atherosclerotic disease. In line with our findings, another study also reported significant improvements in functioning in post-operative abdominal aortic aneurysma patients, which returned to population norms in long-term survivors [11].

In our study, mental functioning was similar to population norms in the acute phase of recovery from a vascular event, but declined during a four year follow-up period. Other studies reported an increased prevalence of mood disturbances already in the acute phase in patients hospitalized for ischemic cardiac or cerebrovascular events [33,34]. One explanation for our findings could be that in the acute phase of an atherosclerotic event, subjective well-being is dominated by the substantial impairments in physical functioning, whereas awareness of the emotional consequences arises after recovery of physical functioning. An alternative explanation could be that the course of mental functioning in patients with symptomatic atherosclerotic disease depends on the severity of the atherosclerotic event. Relatively few patients were included with severe atherosclerotic disease in our study, which could contribute to the different findings in the course of mental functioning between our study and others.

The underlying mechanisms contributing to a lower HRQoL in patients with symptomatic atherosclerotic disease are unclear. It has been suggested that a lower HRQoL could result from direct complications of the disease or treatment of underlying vascular risk factors, or from raised awareness of the disease [35]. An alternative mechanism contributing to a lower perceived HRQoL could be the presence of co-occurring intracerebral atherosclerotic

changes, characterized by WML on MRI. WML are strongly associated with the presence of common vascular risk factors, including increased age, hypertension and diabetes mellitus [36-38]. Although the exact underlying pathophysiological mechanisms remain unclear, arteriosclerotic changes to the cerebral small vasculature, with consequent ischemia, apoptosis and blood-brain barrier alterations are thought to be involved in the formation and progression of WML [39]. Although WML are often asymptomatic MRI findings, increased volume and progression of WML have been previously associated with an increased risk of functional decline [14], depression [16] and cognitive impairment [18,19]. WML are thought to account for the increased risks of functional decline and mood disorders by disrupting brain pathways that are involved in the regulation of physical and emotional responses [40]. Although we did not formally measure depression, our finding that increased WML activity was associated with a greater decline in mental functioning may be interpreted as being supportive of this 'vascular depression' hypothesis [40]. Greater progression of WML volume contributed to a stronger decline in mental functioning in all patients except for patients with cerebrovascular disease. This finding is somewhat counterintuitive but may be explained by our finding of little improvement in physical functioning in patients with cerebrovascular disease. It could be that as a result of the substantial impairments and disability already associated with stroke lesions, increased progression of WML volume does not substantially contribute to the decline in mental functioning in these patients.

In summary, in patients with different manifestations of atherosclerotic disease we found that physical functioning was mainly impaired in the acute phase after a symptomatic atherosclerotic event and improved during four years of follow-up, although improvement in physical functioning remained substantially lower in patients with cerebrovascular disease. Mental functioning was relatively unimpaired in the early phase, but declined in the four years thereafter. Greater progression of white matter lesion volume contributed to an even stronger decline in mental functioning in patients with symptomatic atherosclerotic disease. Considering the substantial impact on well-being and previously reported increased risk of adverse events associated with lower mental and physical functioning, further research should investigate whether modification of WML through better control of vascular risk factors could influence the course of HRQoL in patients with symptomatic atherosclerotic disease.

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Chapter 2.2

Self-rated health status as a risk factor for future vascular events and mortality in patients with symptomatic and asymptomatic atherosclerotic disease. The SMART study

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Abstract

Objectives

Lower self-rated health status has been associated with worse prognosis in patients with coronary artery disease (CAD). We investigated the influence of self-rated physical and mental health status on the risk of future vascular events and mortality for various locations of symptomatic atherosclerotic disease and asymptomatic disease.

Methods

Patients with CAD (n=2547), cerebrovascular disease (n=1061), peripheral arterial disease (PAD; n=648), abdominal aortic aneurysm (AAA; n=272) and asymptomatic atherosclerotic disease (n=1933) were followed for a median of 4 years for the occurrence of a new vascular event or death. Self-rated health status was assessed with the Short Form-36 physical and mental component summary scales. Cox regression models were used to estimate associations between health status and vascular events and death, adjusted for age, sex, vascular risk factors and intima media thickness.

Results

In the total population, lower self-rated physical health status (per 10-point decrease) increased the risk of vascular events (HR=1.37, 95% CI 1.24-1.52), all-cause (HR=1.45, 95% CI 1.29-1.63) and vascular mortality (HR=1.40, 95% CI 1.20-1.64). A 10-point decrease in mental health status was associated with a modest increase in the risk of vascular events (HR=1.19, 95% CI 1.08-1.32), all-cause (HR=1.19, 95% CI 1.05-1.34) and vascular mortality (HR=1.28, 95% CI 1.09-1.49). Risk estimates of physical and mental health status were highest in patients with asymptomatic atherosclerotic disease, and lowest in those with PAD.

Conclusions

Poorer self-rated physical and mental health status increases the risk of vascular events and mortality in a broad population of patients with symptomatic and asymptomatic atherosclerotic disease.

Introduction

Cardiovascular disease is a major health problem worldwide, with ischaemic heart disease and stroke as leading causes of burden of disease [1]. Patient-rated health status has become increasingly important, due to recent advances in treatment strategies and secondary prevention measures that have led to improved survival of patients with cardiovascular disease [2,3]. Increasing evidence, however, has suggested that self-rated health status is not only an important outcome measure in patients with cardiovascular disease, but also an independent risk factor for hospital readmissions and mortality [4-6].

It remains unclear whether the impact of self-rated health status on the prognosis of patients with cardiovascular disease depends mainly on physical or mental components of well-being. Although the majority of studies have found that lower physical health status is associated with an increased risk of cardiovascular events and mortality [7-10], studies investigating the impact of mental health status have yielded inconsistent findings [7,8,10,11]. In addition, few studies examining the effects of physical and mental health status on the prognosis of patients with cardiovascular disease have investigated which of the separate underlying health domains are the strongest contributors to these associations [10].

Furthermore, previous studies examining the prognostic role of self-rated health status in patients with cardiovascular disease have primarily focused on patients with coronary artery disease (CAD) [4,7-12]. Although CAD, cerebrovascular disease, peripheral arterial disease (PAD) and abdominal aortic aneurysm (AAA) are generally considered to be different expressions of a single underlying disease (i.e. atherosclerosis [13,14]), no studies have investigated whether lower self-rated health status has a comparable influence on the prognosis of patients with different locations of symptomatic atherosclerotic disease. In addition, it is unclear whether lower self-rated health status increases the risk of future vascular events and mortality in individuals without clinical manifestations of atherosclerosis.

The Second Manifestations of ARTerial disease (SMART) study, a large prospective cohort study in patients with symptomatic and asymptomatic atherosclerotic disease, offers a unique opportunity to study the relation between self-rated health status and clinical events in patients with various stages and manifestations of atherosclerotic disease. First we investigated whether lower self-rated physical and mental health status are individual risk factors for future vascular events, all-cause mortality and vascular death in the SMART cohort, as well as which underlying domains of health status showed the strongest association with the future risk of these outcomes in this cohort. Second, we investigated whether the impact of physical and mental health status on the risk of future vascular events, all-cause mortality and vascular death differs between patients with CAD, cerebrovascular disease, PAD, AAA and asymptomatic atherosclerotic disease.

Materials and methods

Participants

Data were used from patients enrolled in the Second Manifestations of ARTerial disease (SMART) study, an ongoing prospective follow-up study that started in 1996. All patients, aged 18-79 years, newly referred to the University Medical Center Utrecht for treatment of symptomatic (manifest CAD, cerebrovascular disease, PAD or AAA) or asymptomatic atherosclerotic disease, were enrolled in the SMART study. Exclusion criteria were: age ≥80 years at inclusion, diagnosis of a terminal malignancy, not being independent in daily activities (Rankin scale >3), not being sufficiently fluent in Dutch, or being referred back to the referring specialist [15]. CAD was defined as a history of coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, or myocardial infarction either previously or at inclusion. Patients with a transient ischemic attack or stroke at inclusion and patients who reported stroke in the past were considered to have cerebrovascular disease. PAD was defined as a history of surgery or angioplasty of the arteries supplying the lower extremities, or intermittent claudication or pain at rest at inclusion. AAA was defined as AAA (distal aortic diameter ≥3 cm) at inclusion or previous surgery for AAA. Patients with asymptomatic atherosclerotic disease, defined as presence of risk factors for atherosclerosis, including hypertension, diabetes mellitus, hyperlipidemia and renal insufficiency, and no history of cardiovascular events [15], were referred to the University Medical Center Utrecht because of insufficient response for standard treatment for these risk factors or the presence of multiple risk factors. During a 1-day visit to our medical center, physical examination, ultrasonography of the carotid arteries, blood and urine sampling were performed. Risk factors and medical history were assessed with questionnaires. The Short-Form 36-item (SF-36) questionnaire was added in October 2001. The SMART study was approved by the ethics committee of our institution and written informed consent was obtained from all participants. For the current study, 5877 patients with available data from the SF-36 questionnaire, were included before 1 March 2010.

Self-rated physical and mental health status

At baseline, patients completed the SF-36, a widely used and well-validated questionnaire for assessing multidimensional aspects of self-rated health status [16]. The SF-36 is organized into eight multi-item health domains: physical functioning, role limitations due to physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health. Raw scale scores are transformed into a variable ranging from 0-100, with lower scores indicating lower levels of well-being. As measure of physical health status, the first four domains were combined into a physical component summary scale. The last four domains were combined into a mental component summary scale as measure of mental health status [17]. Component scales were positively

scored and normalized to a general population mean of 50 with standard deviation of 10, with lower scores indicating lower levels of well-being. As previously recommended, a 10-point decrease in the physical and mental component scores was considered clinically relevant [18,19].

Outcomes

The occurrence of new vascular events was continuously monitored by asking the patients to complete a questionnaire every 6 months to provide information on hospitalization and outpatient clinic visits. If a cardiovascular event was reported in the questionnaire or a death was reported by a family member, original source documents were retrieved and reviewed to confirm the occurrence of cardiovascular disease or determine the cause of death. All possible events were audited independently by three physicians of the Outcome Event Committee. Patients were followed until death or refusal of further participation. The main outcomes of interest for this study were the occurrence of (recurrent) vascular events, all-cause mortality and vascular death (table 1).

Vascular risk factors

During the visit to the medical center, an overnight fasting venous blood sample was taken to determine glucose and lipid levels. Height and weight were measured without shoes and heavy clothing, and the body mass index (BMI) was calculated (kg/m^2). Systolic and diastolic blood pressures (mm Hg) were measured twice with a sphygmomanometer and averaged. Hypertension was defined as mean systolic blood pressure ≥140 mm Hg, mean diastolic blood pressure ≥90 mm Hg, or self reported antihypertensive drug use. Diabetes mellitus was defined as fasting glucose ≥11.1 mmol/L, history of diabetes mellitus, or self reported use of oral antidiabetic drugs or insulin. Hyperlipidemia was defined as total cholesterol >5.0 mmol/L, low-density lipoprotein cholesterol >3.2 mmol/L, or self reported use of lipid lowering drugs. Smoking habits and alcohol intake were assessed with questionnaires. Pack-years of smoking were calculated, and alcohol use was categorized into none or current. Physical activity was assessed according to the intensity and amount of exercise (metabolic equivalents (MET) hours per week), by multiplying time spent on sport activities per week by sport-specific energy expenditure, and was categorized into no (0 MET hours per week), moderate (1-15 MET hours per week; reference category) and vigorous physical activity (>15 MET hours per week) [20]. Ultrasonography was performed to measure the intima-media thickness (IMT) (mm) in the left and right common carotid arteries as a measure of severity of subclinical atherosclerosis, represented by the mean value of six measurements.

Severity of atherosclerotic disease at baseline

In patients with PAD, severity of atherosclerotic disease at baseline was assessed with the Fontaine scale [21]. Stage 1 (pain-free walking distance >200 m) and stage 2 (pain-free walking distance <200 m) were defined as mild or moderate ischaemia, whereas stage 3 (pain at

rest) and stage 4 (ulceration or gangrene) were defined as severe ischaemia. In patients with CAD, disease severity was rated according to the number of coronary arteries with marked atherosclerosis (>70% stenosis or fractional flow reserve <0.80 or treatment of the vessel). One-, two- and three-vessel disease and left main disease with or without right coronary artery involvement were assessed in all CAD patients on the basis of coronary angiography reports. Information was incomplete in some patients, and additional information was obtained from percutaneous coronary intervention or coronary artery bypass grafting reports. For patients with cerebrovascular disease, disease severity was classified with a handicap scale, the modified Rankin Scale (mRS) [22]. For patients with AAA, severe disease was defined as previous surgery for AAA.

Data analysis

We used multiple imputation [23] (10 datasets) to address the missing baseline values in the study sample of 5877 patients, with the statistical programme R (AregImpute). Data were analyzed with SPSS version 17.0 (Chicago, IL, USA), by pooling the 10 imputed datasets. The time between the date of baseline screening and death, loss to follow-up or end of follow-up before 1 March 2010, whichever came first, was calculated to establish the follow-up time. Cox proportional hazard analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of self-rated physical and mental health status (per 10-point decrease) and the composite vascular outcome, all-cause mortality and vascular death, respectively. Associations were adjusted for age and sex in model 1. We additionally adjusted for physical activity, smoking, alcohol use, BMI, hyperlipidemia, hypertension, diabetes mellitus and IMT in model 2. In model 3, associations of physical health status with outcomes were adjusted for mental health status, and associations between mental health status and outcomes were adjusted for physical health status.

Next, to examine which individual health domains showed the strongest association with the risk of future vascular events, all-cause mortality and vascular death, we investigated associations of the eight individual health domains as independent variables, and the three outcomes as dependent variables. The individual health domains were analyzed as dichotomous variables (lowest quartile vs. three higher quartiles), to investigate whether patients with most impairments had worse prognosis than patients with less or no impairments. Adjustment for confounders in models 1 and 2 was as described above. In model 3, associations of physical health domains with outcomes were adjusted for the four mental health domains, and associations between mental health domains and outcomes were adjusted for physical health domains.

Then, we repeated the analyses among patients with different locations of symptomatic atherosclerotic disease (CAD, cerebrovascular disease, PAD and AAA) and asymptomatic

atherosclerotic disease to investigate whether the effect of self-rated health status on the prognosis differs between these patient groups. Models 1 to 3 were adjusted for confounders as described above, with the exception that model 2 was additionally adjusted for more than one location of symptomatic atherosclerotic disease, as various locations of disease can occur in individual patients.

Finally, we performed a sensitivity analysis by repeating all analyses after exclusion of patients with severe atherosclerotic disease at baseline (n=124). Severe atherosclerotic disease was defined as cerebrovascular disease with mRS grade ≥2, PAD with Fontaine grade ≥3 or surgery for AAA [14]. The proportional hazards assumption was satisfied on the basis of log versus -log survival plots.

Results

At baseline, mean age was 56±12 years and 67% of the sample was male (table 2). The median score was 44 (10^{th}-90^{th} percentile 27-56) for physical health status, which is somewhat lower than the average for the general population, and 52 (10^{th}-90^{th} percentile 33-61) for mental health status. When comparing patients with different locations of symptomatic atherosclerotic disease, those with PAD reported worse physical health status than other patients (Table 2), particularly in the domains of physical functioning and bodily pain (Figure 1). By contrast, mental health status did not substantially differ between patient groups.

Table 1 Definition of Outcomes

Ischaemic stroke	Relevant clinical features causing an increase in impairment of at least one grade on the modified Rankin scale, without signs of haemorrhage on repeat brain imaging.
Myocardial infarction	At least two of the following criteria: (I) Chest pain for at least 20 min, not disappearing after administration of nitrates; (II) ST-elevation > 1 mm in two contiguous leads or a left bundle branch block on the electrocardiogram; (III) Creatinine kinase (CK) elevation of at least two times the normal value of CK and a myocardial band-fraction > 5% of the total CK.
Vascular mortality	Sudden death: unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours in the presence of further convincing evidence. Death from stroke, myocardial infarction, congestive heart failure, or rupture of abdominal aortic aneurysm. Vascular death from other causes.
Composite vascular outcome	A composite of stroke, myocardial infarction, retinal infarction, and vascular mortality.
All-cause mortality	Death from any cause.

Table 2 Baseline characteristics of the SMART study

	Total sample (n=5877)	CAD (n=2547)*	Cerebrovascular disease (n=1061)*	PAD (n=648)*	AAA (n=272)*	Asymptomatic atherosclerotic disease (n=1933)
Age† (years)	56 ± 12.4	61 ± 9.7	59 ± 11.3	59 ± 10.3	64 ± 10.2	49 ± 13.0
Male sex (%)	67	81	60	67	82	53
Smoking (pack-years)‡	11 (0-43)	13 (0-46)	13 (0-48)	25 (0-56)	23 (0-56)	4 (0-32)
BMI† (kg/m^2)	27.0 ± 5.0	26.9 ± 3.8	26.7 ± 4.3	26.5 ± 4.2	26.2 ± 3.8	26.8 ± 5.2
Alcohol use (%)	81	83	83	83	82	79
Physical activity (%):						
- None (0 MET hours per week)	58	60	61	68	73	54
- Moderate (1-15 MET hours per week)	22	20	20	18	14	28
- Vigorous (>15 MET hours per week)	19	20	19	14	14	19
Hypertension (%)	68	66	72	73	70	68
Diabetes mellitus (%)	19	19	16	20	18	22
Hyperlipidemia (%)	90	96	89	91	87	83
IMT† (mm)	0.87 ± 0.26	0.91 ± 0.26	0.92 ± 0.29	0.97 ± 0.30	0.96 ± 0.30	0.78 ± 0.22
Physical health status‡	44 (27-56)	43 (28-55)	43 (27-56)	36 (21-51)	40 (23-55)	49 (30-58)
Mental health status‡	52 (33-61)	53 (35-61)	50 (31-61)	54 (33-63)	54 (32-62)	52 (32-60)

CAD, Coronary artery disease; PAD, Peripheral arterial disease; AAA, Abdominal aortic aneurysm; BMI, Body mass index; MET, Metabolic equivalent; IMT, Intima media thickness

* Various locations of symptomatic atherosclerotic disease can occur within one patient

† Mean ± SD

‡ Median, (10^{th}-90^{th} percentile)

Percentage of missing values before imputation: alcohol use: 0.7%, hyperlipidemia: 0.5%, hypertension: 0.6%, physical and mental health status: 4.3%, all other variables: 0.0 %

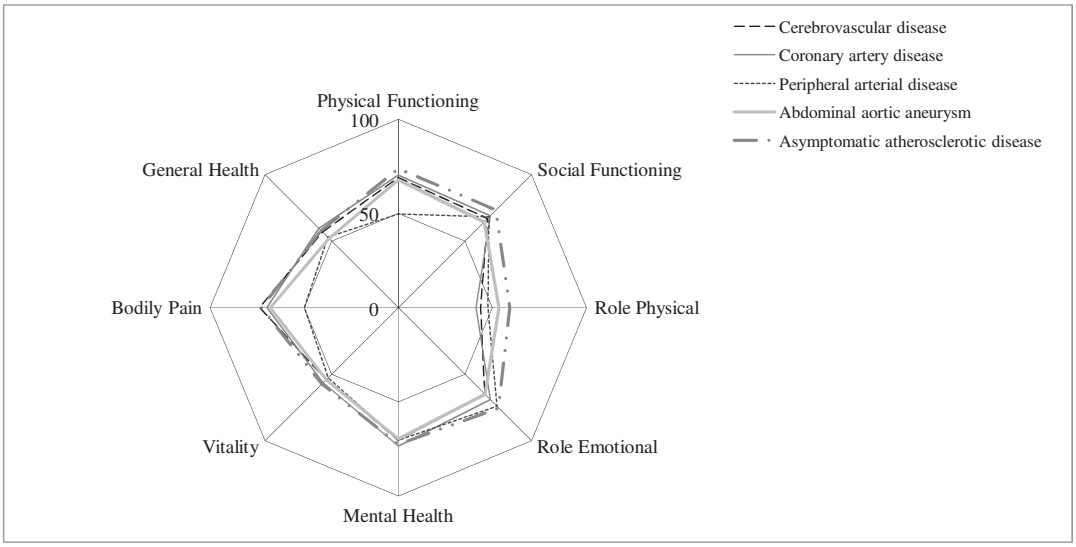

Figure 1 Radar chart illustrating mean scores of individual health domains, for patients with different locations of symptomatic atherosclerotic disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease, and abdominal aortic aneurysm) and asymptomatic atherosclerotic disease, adjusted for age and sex.

Physical and mental health status, vascular events and mortality

During a median follow-up time of 4.0 (range 0.1-8.4) years, 251 (4.3%) patients died; 135 of these deaths were due to a vascular cause. In addition, 315 (5.4%) experienced a vascular event. In the total cohort, a 10-point decrease in physical health status increased the risk of new or recurrent vascular events (HR=1.35, 95% CI 1.22-1.50), all-cause mortality (HR=1.42, 95% CI 1.26-1.60) and death due to a vascular cause (HR=1.36, 95% CI 1.16-1.59) (Table 3, model 2). A 10-point decrease in mental health status also increased the risk of vascular events (HR=1.19, 95% CI 1.08-1.32), all-cause mortality (HR=1.19, 95% CI 1.07-1.31) and vascular death (HR=1.27, 95% CI 1.09-1.48) (Table 3, model 2). Additional adjustment for physical or mental health status did not substantially change the HR values (Table 3).

Underlying health domains, vascular events and mortality

When separate underlying health domains were distinguished, patients in the lowest quartile of any of the four domains of physical health status, representing the most severe impairment of physical health, were at significantly higher risk of vascular events, all-cause mortality and death due to vascular causes than patients in the three highest quartiles (Table 4, model 2). For all outcomes, associations were stronger for the domains of physical functioning and general health perception than for role limitations due to physical health problems and bodily pain. Associations were attenuated after additional adjustment for mental health domains, but remained statistically significant for domains of physical functioning and general health perception (data not shown).

Table 3 Relationship between self-rated physical and mental health status and outcome events(n=5877)

			Hazard Ratio (95% CI)		
	No. of events	No. of person years	Model 1	Model 2	Model 3
Vascular events					
Physical health status*			1.42 (1.28–1.56)	1.35 (1.22–1.50)	1.37 (1.24–1.52)
Mental health status*	315	22798	1.21 (1.09–1.34)	1.19 (1.08–1.32)	1.21 (1.10–1.34)
All-cause mortality					
Physical health status*			1.47 (1.32–1.65)	1.42 (1.26–1.60)	1.45 (1.29–1.63)
Mental health status*	251	23319	1.21 (1.08–1.36)	1.19 (1.07–1.31)	1.21 (1.09–1.33)
Vascular mortality					
Physical health status*			1.46 (1.26–1.70)	1.36 (1.16–1.59)	1.39 (1.18–1.63)
Mental health status*	135	23319	1.30 (1.11–1.52)	1.27 (1.09–1.48)	1.29 (1.11–1.51)

* Per 10-point decrease

Model 1: Adjusted for age and sex

Model 2: Additionally adjusted for physical activity, smoking (pack-years), alcohol consumption, body mass index, hyperlipidemia, hypertension, diabetes mellitus and intima media thickness

Model 3: additionally adjusted for mental health status (for associations between physical health status and outcomes) or physical health status (for associations between mental health status and outcomes)

In addition, patients in the lowest quartile of any of the four domains of mental health status, representing the most severe impairment of mental health, were at significantly higher risk of vascular events, all-cause mortality and vascular death than patients in the three highest quartiles (Table 4, model 2). Associations were slightly stronger for domains of social functioning and vitality than for role limitations due to emotional problems and mental health, although these differences in HR values were less apparent than for the different domains of physical functioning. Associations were attenuated after additional adjustment for physical health domains, but remained borderline significant for the domain of social functioning (data not shown).

Self-rated health status, vascular events and mortality in different groups of patients with symptomatic and asymptomatic atherosclerotic disease

In Cox regression models across different locations of atherosclerotic disease, risk estimates of the relation between self-rated physical health status and vascular events and vascular death were highest in patients with asymptomatic atherosclerotic disease, and the lowest risk estimates were found in patients with PAD (Table 5). A similar trend was observed for mental health status (Table 5).

Table 4 Relations between separate underlying health domains and outcome events (n=5877)

	Vascular events	All-cause death	Vascular death
	Hazard Ratio† (95% CI)	Hazard Ratio† (95% CI)	Hazard Ratio† (95% CI)
Physical health domains*			
Physical functioning	1.89 (1.48–2.41)	2.39 (1.82–3.12)	2.19 (1.50–3.21)
Role limitation: physical	1.56 (1.24–1.96)	1.45 (1.13–1.88)	1.57 (1.11–2.23)
Bodily pain	1.37 (1.08–1.73)	1.39 (1.05–1.83)	1.17 (0.80–1.70)
General health	1.95 (1.55–2.46)	2.19 (1.69–2.84)	2.50 (1.74–3.60)
Mental health domains*			
Social functioning	1.85 (1.47–2.34)	1.90 (1.46–2.47)	2.10 (1.48–3.00)
Role limitation: emotional	1.48 (1.16–1.90)	1.42 (1.08–1.86)	1.89 (1.31–2.74)
Mental health	1.38 (1.08–1.76)	1.69 (1.29–2.21)	1.63 (1.11–2.39)
Vitality	1.71 (1.35–2.18)	1.80 (1.37–2.36)	1.71 (1.18–2.50)

* Lowest quartile versus three highest quartiles

† Adjusted for age, sex, physical activity, smoking (pack-years), alcohol consumption, body mass index, hyperlipidemia, hypertension, diabetes mellitus and intima media thickness

Exclusion of patients with severe atherosclerotic disease

Excluding patients with severe atherosclerotic disease (n=124) did not change any effect estimates or significance levels of the associations between physical and mental health status and the composite vascular outcome, all-cause mortality and vascular death in the total cohort or within different patient groups (data not shown).

Table 5 Relations between self-rated health status and events for different locations of symptomatic and asymptomatic atherosclerotic disease

	CAD (n=2547)	**Cerebrovascular disease (n=1061)**	**PAD (n=648)**	**AAA (n=272)**	**Asymptomatic atherosclerotic disease (n=1933)**
	Hazard ratio‡ (95% CI)	Hazard ratio‡ (95% CI)	Hazard ratio‡ (95% CI)	Hazard ratio‡ (95% CI)	Hazard ratio‡ (95% CI)
Vascular events*	***(154/ 9264)***	***(93/ 3875)***	***(63/ 2594)***	***(43/ 1040)***	***(49/ 8087)***
Physical health status†	1.29 (1.11–1.51)	1.23 (1.01–1.50)	1.04 (0.81–1.33)	1.15 (0.85–1.55)	1.52 (1.16–1.99)
Mental health status†	1.12 (0.96–1.29)	1.18 (0.98–1.40)	1.04 (0.83–1.30)	1.22 (0.92–1.62)	1.24 (0.96–1.61)
All-cause mortality*	***(119/ 9528)***	***(67/ 4054)***	***(60/ 2665)***	***(40/ 1095)***	***(37/ 8156)***
Physical health status†	1.35 (1.13– 1.62)	1.39 (1.11–1.75)	1.10 (0.85–1.41)	1.57 (1.11–2.22)	1.26 (0.94–1.70)
Mental health status†	1.19 (1.02–1.40)	1.11 (0.89–1.38)	1.07 (0.84–1.36)	1.32 (0.97–1.78)	1.28 (0.95–1.71)
Vascular mortality*	***(65/ 9528)***	***(38/ 4054)***	***(38/ 2665)***	***(29/ 1095)***	***(17/ 8156)***
Physical health status†	1.28 (1.00– 1.62)	1.19 (0.87–1.62)	1.12 (0.82–1.53)	1.17 (0.79–1.73)	1.37 (0.87–2.15)
Mental health status†	1.20 (0.97–1.49)	1.18 (0.88–1.59)	1.10 (0.83–1.47)	1.47 (1.04–2.09)	1.61 (1.03–2.52)

CAD, Coronary artery disease; PAD, Peripheral arterial disease; AAA, Abdominal aortic aneurysm

* Number of events/ number of person-years; † Per 10-point decrease

‡ Adjusted for age, sex, physical activity, smoking (pack-years), alcohol consumption, body mass index, hyperlipidemia, hypertension, diabetes mellitus, intima media thickness and concurrent locations of symptomatic atherosclerotic disease

Discussion

The results of this study show that lower self-rated levels of physical as well as mental health status are strong independent risk factors for vascular events and mortality in a cohort of patients with symptomatic and asymptomatic atherosclerotic disease. Impairment in domains of general health and physical and social functioning were the strongest contributors to a poor prognosis. Risk estimates of the effect of lower self-rated physical and mental health status on adverse events were slightly higher for patients with asymptomatic atherosclerotic disease compared with other patient groups, whereas the lowest risk estimates were observed in patients with PAD.

The finding that lower self-rated physical health status increased the risk of cardiovascular events and all-cause mortality is in line with most studies in CAD patients [4,7-11]. Proposed mechanisms accounting for the relation between self-rated physical health and clinical outcome include the presence of underlying vascular risk factors, such as hypertension, diabetes mellitus, dietary patterns, alcohol use and smoking. Nevertheless, consistent with other studies [7,24,25] we observed that adjustment for these variables did not change the relation between self-reported physical health status and adverse events. Alternatively, lower self-rated physical health status could either be an indicator of inefficiency of medical treatment in patients with cardiovascular disease [26], or a reflection of undetected biological processes directly affecting survival [4] such as stress, which could lead to increased mortality through abnormal sympathetic activity-induced cardiac arrhythmias. However, our data not support the latter hypothesis, as the relation between physical health status and vascular mortality was not primarily driven by the occurrence of sudden death (data not shown). On the other hand, in line with previously observed relations between physical activity and mortality risk [27], our finding that impairments in physical functioning and general health perception were the main contributors to the risk of vascular events and mortality suggests that physical inactivity may be an important underlying mechanism in the relation between lower physical health status and adverse events. Although additional adjustment for physical activity resulted in a modest attenuation of the effect, this did not however influence any significance levels.

Although a relation between depression and mortality has been well established in patients with cardiovascular disease [28,29], the impact of more subtle impairments in mental well-being on the prognosis of these patients seems less straightforward. Of the studies in CAD patients, some have found that lower self-reported mental health status increases the mortality risk [10], whereas others could not replicate this relationship [7,11] or even reported a positive effect on mortality risk [8]. We observed that lower self-rated mental health status was associated with a modest increase in the risk of future vascular events and mortality.

However, it has been shown that the two underlying health domains (social functioning and vitality) that contributed most strongly to this association are also strongly correlated with physical health status [17], and additional adjustment for physical health status attenuated the effect of these domains on clinical outcome.

Our study is the first to extrapolate the finding that lower self-rated health status increases the risk of hospital readmissions and mortality in CAD patients [4,8,10,11] to a much broader population of patients with cardiovascular disease. An interesting finding was that the risk of both vascular and all-cause death was increased, suggesting that lower self-rated health status is not only associated with fatal and non-fatal vascular events but also with death from non-vascular causes. Our observation that risk estimates of the relation between self-rated health status and outcome were higher for patients with asymptomatic atherosclerotic disease compared to those with symptomatic atherosclerotic disease should be interpreted with caution, as the selection of patients based on the occurrence of cardiovascular disease at baseline may have introduced 'index event' bias, contributing to an underestimation of the effect of self-rated health status on recurrent vascular events in patients with symptomatic atherosclerotic disease [30]. In addition, the severity of atherosclerotic disease in our cohort was relatively mild, as few (2.1%) patients with severe atherosclerotic disease were included. Because risk factors for atherosclerosis will be more complex in asymptomatic patients referred to an academic centre, this may have led to a smaller difference between patients with symptomatic and asymptomatic atherosclerotic disease. Furthermore, we found substantially lower risk estimates of the relation between self-rated physical health status and adverse events in PAD patients compared to patients with other locations of symptomatic atherosclerotic disease. One possible explanation for this is that the effect of a 10-point decrease in physical health status may be more limited in patients with PAD because of the more pronounced physical impairment and disability in these patients, as reflected by lower baseline levels of physical health status (Table 2; Figure 1). Alternatively, the overlap in confidence intervals between different patient groups suggests that differences in risk estimates may also be partially explained by chance.

Major strengths of our study include the large sample size, extensive information on cardiovascular risk factors and the extent of clinical and subclinical atherosclerosis, rigorous monitoring of clinical outcome and statistical adjustment for clinical and underlying subclinical atherosclerotic disease. In addition, separate underlying domains of health status were analysed in only one other study in PAD patients [10].

A limitation of our study is that despite the large sample size, there were relatively few patients with PAD, cerebrovascular disease or AAA. Although similar associations were

found in patients with CAD, cerebrovascular disease and AAA, the relatively low number of patients with locations of symptomatic atherosclerotic disease other than CAD contributed to large confidence intervals and could have resulted in non-significant relations in these patients. Furthermore, it is unclear whether the four different categories of symptomatic atherosclerotic disease share the same severity. Excluding patients with severe atherosclerotic disease did not however change the relationship between self-rated health status and outcome. Moreover, comparing PAD with other locations of symptomatic atherosclerotic disease is complicated because the Fontaine classification is based solely on pain symptoms, whereas these symptoms do not play a role in other disease severity classifications. Finally, self-rated health status was only assessed at baseline, thereby preventing us from studying the influence of changes in well-being on clinical prognosis.

Although the application of patient-rated instruments of health status has been proposed as a useful tool in the risk stratification and surgical decision-making for patients with CAD [7,9], our findings suggest it may benefit a more diverse population of patients with symptomatic as well as asymptomatic atherosclerotic disease. Assessment of self-rated health status is an easy and non-invasive method for the identification of patients at high risk of adverse events, and may be particularly applicable for use in patients with atherosclerotic disease considering that they undergo regular routine healthcare visits. Although preliminary studies have reported promising results [25,31], long-term studies are needed to examine whether the reversal of poor self-rated health status, through positive changes in lifestyle factors including physical activity, could improve the prognosis of patients at high risk of adverse events.

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Chapter 2.3

Mood problems increase the risk of mortality in patients with lacunar infarcts. The SMART-MR study

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Abstract

Objectives

A relation between depression and mortality has been well-established, but underlying mechanisms are poorly understood. We investigated the influence of cerebral small-vessel disease (CSVD), characterized by white matter lesions (WML) and lacunar infarcts, on the relation between mood problems and mortality.

Methods

Mood problems were assessed with the Mental Component Summary (MCS) of the SF-36 in 1110 patients with symptomatic atherosclerotic disease (59±SD10 years) from the SMART-MR study. Volumetric WML estimates were obtained with 1.5T MRI; lacunar infarcts were scored visually. Cox regression models were adjusted for age, sex, vascular risk factors, physical functioning, antidepressant use and infarcts. Patients were followed for a median of 6.0 (range 0.2-8.7) years. We adjusted for CSVD to examine whether it may be an intermediate or confounding factor. Second, we added interaction terms to investigate whether associations differed between patients with CSVD (absent/present).

Results

Patients in the lowest quartile of MCS score, representing most severe mood problems, were at higher, although not statistically significant, risk of death (HR=1.47, 95% CI 0.94-2.30) compared to patients in higher quartiles. Adjustment for CSVD did not change this association. Lacunar infarcts, but not WML, modified the association of mood problems with mortality (p-value for interaction=0.01); mood problems strongly increased the risk of mortality in patients with lacunar infarcts (HR=2.75, 95% CI 1.41-5.38), but not in those without lacunar infarcts (HR=0.78, 95% CI 0.39-1.57).

Conclusions

Patients with lacunar infarcts may be especially vulnerable for the effect of mood problems on poor outcome.

Introduction

A relation between depression and mortality has been well-established in patients with [1-5] and without cardiovascular disease [6]. Several pathophysiological factors have been investigated as possible mechanisms underlying the relation between cardiovascular disease, depression and mortality, including autonomic nervous system dysregulation [7], increased platelet activation [8], inflammatory processes [9], presence of cardiac risk factors [10,11], and nonadherence to cardiac prevention and treatment regimens [12,13]. Despite these efforts, it remains uncertain which of these factors, if any, can explain the relation between cardiovascular disease, depression and mortality [14].

An alternative mechanism that may play a role in the relation between depression and mortality is the presence of cerebral small-vessel disease (CSVD) [15]. CSVD is particularly common in patients with cardiovascular disease [16], and is thought to result from arteriosclerotic changes to the cerebral small vasculature, leading to ischemia and concomitant incomplete infarction or necrosis [17]. On brain magnetic resonance imaging (MRI), CSVD is characterized by the presence of white matter lesions (WML) and lacunar infarcts.

In line with community-based studies [18-20], we recently demonstrated that WML and lacunar infarcts are independent risk factors for vascular and non-vascular death in patients with symptomatic atherosclerotic disease [21]. No studies however directly investigated whether WML and lacunar infarcts influence the relation between depressive symptoms and mortality. As recently shown [22], depression is associated with an increased progression of CSVD, suggesting that an increased risk of mortality could result as a direct consequence of CSVD. Alternatively, increasing evidence has suggested that CSVD might lead to an increased risk of depression [23], through the disruption of mood-regulating frontal-subcortical pathways, as postulated by the 'vascular depression' hypothesis [24,25]. 'Vascular depression' is thought to represent a unique disease entity, with distinctive clinical characteristics and a substantially poorer prognosis than non-vascular depression [26].

Our aim was to examine whether the presence of WML and lacunar infarcts could play a role in the relation between mood problems and the risk of death, including vascular and non-vascular death, in patients with symptomatic atherosclerotic disease. We expect that as a result of their high vascular burden, these patients are more vulnerable for the presence of cerebrovascular changes than the general population.

Materials and methods

Participants

Data were used from the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study aimed to investigate brain changes on MRI in 1309 independently living patients, newly referred to the University Medical Center Utrecht between May 2001 and December 2005 with manifest peripheral arterial disease, coronary artery disease, cerebrovascular disease or abdominal aortic aneurysm and without MR contraindications. Details of the design and participants have been described elsewhere [27]. During a 1-day visit to our medical center, MRI of the brain, physical examination, blood and urine sampling were performed. Risk factors, medical history, and functioning were assessed with questionnaires. The SMART-MR study was approved by the ethics committee of our institution and written informed consent was obtained from all participants. For the current study, 1141 patients with available data on mood problems were included, because the SF-36 questionnaire was introduced in January 2002.

Mood problems

At baseline, patients completed the Short Form-36 (SF-36) Medical Outcomes Study Health Survey [28]. The SF-36 encompasses 36 items organized into eight health dimensions or scales: physical functioning, role limitations due to physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health. The last four scales were aggregated into a Mental Component Summary (MCS) scale, which was positively scored and normalized to a general population mean of 50 with standard deviation of 10, with lower scores indicating lower levels of well-being [29]. The MCS has been shown to be a good indicator of mood problems both in general and diseased populations [30-32].

Magnetic resonance imaging protocol

MR investigations were performed on a 1.5-Tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE): 235/2 ms; flip angle, 80º), a transversal T2-weighted turbo spin-echo sequence (TR/TE: 2200/11 ms and 2200/100 ms; turbo factor 12), a transversal T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI): 6000/100/2000 ms) and a transversal inversion recovery (IR) sequence (TR/TE/TI: 2900/22/410 ms) (field of view 230x230 mm; matrix size, 180x256; slice thickness, 4.0 mm; no gap; 38 slices).

Brain segmentation

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique has been described elsewhere [33,34]. The segmentation program distinguishes gray matter, white matter, sulcal and ventricular cerebrospinal fluid (CSF), and lesions. The results of the segmentation analysis were visually checked for the presence of infarcts and adapted if necessary to make a distinction between WML and infarct volumes. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, the volumes of WML and infarcts. All volumes cranial to the foramen magnum were included. As a result, the total brain volume includes the cerebrum, brainstem and cerebellum. Total intracranial volume (ICV) was calculated by summing the total brain volume and the volumes of the sulcal and ventricular CSF.

Infarcts and white matter lesions

The whole brain was visually searched for infarcts by a trained investigator and a neuroradiologist. Raters were blinded to all clinical information. Discrepancies in rating were re-evaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images in order to distinguish them from WML. Dilated perivascular spaces were distinguished from infarcts on the basis of their location, form, and the absence of gliosis. The location, affected flow territory and type were scored for every infarct. We defined lacunar infarcts as infarcts sized 3 to 15 mm in diameter and located in the subcortical white matter, thalamus, basal ganglia or brainstem. WML volumes obtained with the segmentation program were summed to obtain total WML volume. Volumes of WML were normalized for ICV, and expressed as percentage of ICV.

Outcome assessment

The outcome of interest for this study was death from vascular cause or other. Patients were sent a questionnaire every six months to provide information on hospitalization and outpatient clinic visits. If family members reported the death of a patient, original source documents were retrieved and reviewed to determine the date and cause of death. All events were audited independently by three physicians of the Endpoint Committee. Patients were followed until death or refusal of further participation. Vascular death was defined as sudden death (unexpected cardiac death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence); death from stroke, myocardial infarction, congestive heart failure, or rupture of abdominal aortic aneurysm; or vascular death from other causes. Non-vascular death was defined as fatal malignancy; fatal infection; non-natural death; or non-vascular death from other causes.

Other variables

During the visit to the medical center, an overnight fasting venous blood sample was taken to determine glucose and lipid levels. Height and weight were measured without shoes and heavy clothing, and body mass index (BMI) was calculated (kg/m^2). Systolic and diastolic blood pressures (mm Hg) were measured twice with a sphygmomanometer and averaged. Hypertension was defined as mean systolic blood pressure ≥160 mm Hg, mean diastolic blood pressure ≥95 mm Hg, or self-reported antihypertensive drug use. Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/L, or self-reported use of oral antidiabetic drugs or insulin. Hyperlipidemia was defined as total cholesterol >5.0 mmol/L, low-density lipoprotein cholesterol >3.2 mmol/L, or self-reported use of lipid lowering drugs. Smoking habits, alcohol intake and antidepressant use were assessed with questionnaires. Pack-years of smoking was calculated, and alcohol use was categorized into never, past, and current. Physical functioning was assessed with the Physical Component Summary scale of the SF-36 questionnaire [29]. Ultrasonography was performed to measure intima-media thickness (IMT) (mm) in the left and right common carotid arteries as a measure of the severity of subclinical atherosclerosis, and was represented by the mean value of six measurements.

Study sample

Of the 1141 patients included, 31 were excluded due to missing MRI data (irretrievable MRI data (n=19), missing FLAIR images (n=12)), leaving 1110 patients for analysis.

Data analysis

We used multiple imputation [35] (10 datasets) to address the missing baseline values in the study sample of 1110 patients, using the statistical programme R (AregImpute). Data were analyzed using SPSS version 17.0 (Chicago, IL, USA), by pooling the 10 imputed datasets.
The time between date of MRI-scan until death, loss to follow-up or end of follow-up in March 2010, whichever came first, was calculated to establish the follow-up time. Univariate analyses were used to compare baseline characteristics between patients in the lowest quartile of MCS score, representing most severe mood problems, and the three highest quartiles.

Cox proportional hazard analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of mood problems with all-cause mortality. Mood problems were analyzed as a categorical variable (lowest quartile (<43.1) vs. the three highest quartiles of MCS score), and as a continuous variable to increase precision (per SD decrease in MCS score). Associations were adjusted for age and sex in model 1. In model 2, we additionally adjusted for smoking, alcohol use, BMI, hyperlipidemia, hypertension, diabetes mellitus, IMT and physical functioning, because it is not clear to what extent these

factors are confounders or preceding factors in the pathway between mood problems and mortality, or both. We additionally adjusted for antidepressant use and presence of cortical or large subcortical infarcts on MRI in model 2. In additional analyses, we investigated the effect of mood problems on mortality from vascular and non-vascular death separately.

To investigate whether CSVD could be an intermediate or confounding factor in the pathway between mood problems and mortality, we additionally adjusted for total WML volume (% of ICV) and the presence of lacunar infarcts in model 3.

In addition, we investigated whether the association of mood problems with all-cause mortality was modified by CSVD by adding interaction terms (mood problems*lacunar infarcts; mood problems*WML) to model 3. If a significant interaction was found, the analyses were repeated within strata of lacunar infarcts (present vs. absent) and WML volume (highest quartile vs. the three lowest quartiles). In addition, cumulative hazard curves for all-cause death were calculated for combined categories of mood problems (lowest quartile of MCS score vs. three highest quartiles) and lacunar infarcts (present vs. absent), and for combined categories of mood problems (lowest quartile of MCS score vs. three highest quartiles) and WML volume (highest quartile vs. three lowest quartiles). The proportional hazards assumption was satisfied on the basis of log-minus-log survival plots.

As final step, we examined whether the influence of lacunar infarcts on the relation between mood problems and mortality depended on the number of lacunar infarcts (0, 1, ≥2).

Results

At baseline, mean age was 59±10 years and 78% of the sample was male (table 1). Mean MCS score was 52 (10^{th}-90^{th} percentile, 34-61). In total, 107 patients died, of whom 52 of vascular cause, during a median follow-up time of 6.0 (range 0.2-8.7) years. The cause of death was yet undefined for one patient. Compared to patients in the three highest quartiles of MCS score, patients in the lowest quartile, representing most severe mood problems, were younger (mean, 56.8 vs. 59.1 years) and more often female (28% vs. 19%), with less current alcohol use (68% vs. 77%), more antidepressant use (10% vs. 4%) and lower physical functioning (median, 39 vs. 42), more often cerebrovascular disease (29% vs. 21%) and less often coronary artery disease (54% vs. 62%) at inclusion (table 1).

Patients in the lowest quartile of MCS score, representing most severe mood problems, were at higher, although not statistically significant, risk of mortality (HR=1.47, 95% CI 0.94-2.30, p=0.09) compared to patients in highest quartiles (table 2). One SD decrease in MCS score was associated with a 1.14 times increased risk (95% CI 0.93-1.40, p=0.20) of mortality

(table 2). When cause of death was distinguished, patients in the lowest quartile of MCS score showed a similar increase in the risk of vascular (HR=1.46, 95% CI 0.76-2.82, p=0.26) and non-vascular death (HR=1.55, 95% CI 0.83-2.88, p=0.17) compared to patients in highest quartiles. Similar associations were found for one SD decrease in MCS score (table 2).

Table 1 Baseline characteristics of the SMART-MR study

	Total sample (n=1110)	Lowest quartile of MCS score (n=278)	Three highest quartiles of MCS score (n=832)	P-value
Age[¥] (years)	59 ± 10	57 ± 10	59 ± 10	<0.01
Male gender (%)	869 (78)	199 (72)	670 (81)	<0.01
Location of symptomatic atherosclerotic disease[£] (%):				
- Coronary artery disease	663 (60)	150 (54)	513 (62)	0.03
- Cerebrovascular disease	252 (23)	81 (29)	171 (21)	<0.01
- Peripheral arterial disease	242 (22)	53 (19)	189 (23)	0.24
- Abdominal aortic aneurysm	91 (8)	20 (7)	71 (9)	0.53
Smoking[†] (pack-years)	19 (0-50)	22 (0-53)	18 (0-49)	0.11
Body mass index[¥] (kg/m^2)	27 ± 3.8	27 ± 3.9	27 ± 3.8	0.33
Alcohol use				
- Never	179 (16)	53 (19)	127 (15)	0.01
- Past	103 (9)	37 (13)	66 (8)	
- Current	828 (75)	188 (68)	640 (77)	
Hypertension (%)	603 (54)	152 (55)	451 (54)	0.95
Diabetes mellitus (%)	230 (21)	65 (24)	164 (20)	0.20
Hyperlipidemia (%)	865 (78)	214 (77)	651 (78)	0.68
Intima media thickness[†] (mm)	0.9 (0.7-1.4)	0.9 (0.7-1.2)	0.9 (0.7-1.3)	0.30
Intracranial volume[¥] (mL)	1457 ± 130	1450 ± 128	1460 ± 130	0.23
Absolute total WML volume[†] (mL)	1.6 (0.5-8.7)	1.6 (0.5-9.1)	1.5 (0.4-8.4)	0.34
Presence of lacunar infarcts (%)	209 (19)	53 (19)	156 (19)	0.93
Presence of cortical or large subcortical infarcts (%)	135 (12)	39 (14)	96 (12)	0.29
Physical functioning[†]	41 (26-55)	39 (28-52)	42 (25-56)	0.01
Antidepressant use (%)	57 (5)	27 (10)	30 (4)	<0.01

[£] The different groups of symptomatic atherosclerotic disease do not add up to the total study sample of 1110, because various locations of symptomatic atherosclerotic disease can occur within one patient.
WML, White matter lesion
[¥] Mean ± SD
[†] Median, (10th-90th percentile)
Percentage of missing values before imputation: hyperlipidemia: 1.0%, intracranial and WML volume: 3.5%, physical functioning: 5.7%, all other variables: 0.0 %

Cerebral small-vessel disease as intermediate or confounding factor

Additional adjustment for WML volume and lacunar infarcts did not attenuate the effect estimates of the relation between mood problems and all-cause mortality (table 2). Also, when the risk of mortality from vascular and non-vascular causes of death was distinguished, no substantial changes in the effect estimates were found (table 2).

Table 2 Cox proportional hazard models of the relationship between mood problems and death (n=1110)

			Hazard Ratio (95% CI)		
	No. of deaths	No. of person years	Model 1	Model 2	Model 3
Mood problems					
Dichotomous (n=278)[£]					
All-cause death	28	1636	1.37 (0.89 – 2.13)	1.47 (0.94 – 2.30)	1.45 (0.92 – 2.28)
Vascular death	13	1636	1.32 (0.70 – 2.49)	1.46 (0.76 – 2.82)	1.50 (0.77 – 2.93)
Non-vascular death	15	1636	1.44 (0.79 – 2.64)	1.55 (0.83 – 2.88)	1.51 (0.81 – 2.83)
Continuous (n=1110)[†]					
All-cause death	107	6607	1.10 (0.90 – 1.34)	1.14 (0.93 – 1.40)	1.15 (0.94 – 1.42)
Vascular death	52	6607	1.05 (0.78 – 1.40)	1.09 (0.81 – 1.47)	1.12 (0.83 – 1.57)
Non-vascular death	54	6607	1.15 (0.87 – 1.52)	1.21 (0.91 – 1.61)	1.21 (0.91 – 1.61)

CI, Confidence interval; SD, Standard deviation; MCS, Mental component summary; WML, White matter lesion; ICV, Intracranial volume

[£] Lowest quartile (<43.1) vs. three highest quartiles of MCS score

[†] Per SD decrease in MCS score

Model 1: adjusted for age and sex

Model 2: additionally adjusted for hypertension, diabetes mellitus, body mass index, smoking (pack-years), alcohol consumption, intima media thickness, physical functioning, antidepressant use and infarcts on MRI

Model 3: additionally adjusted for total WML volume (% of ICV) and presence of lacunar infarcts

Modification by cerebral small-vessel disease

The presence of lacunar infarcts modified the association of mood problems with mortality (mood problems dichotomous*lacunar infarcts p=0.01, mood problems continuous*lacunar infarcts p=0.02). Within patients with lacunar infarcts, patients in the lowest quartile of MCS score, representing most severe mood problems, were at strongly increased risk of all-cause mortality (HR=2.75, 95% CI 1.41-5.38, p=0.01) compared to those in highest quartiles of mood problems (table 3). Also, one SD decrease in MCS score increased the risk of all-cause mortality (table 3). When cause of death was distinguished, similar increases in the risk of vascular and non-vascular death were found per SD decrease in MCS score (table 3). In patients without lacunar infarcts, patients in the lowest quartile of MCS score were not at increased risk of all-cause mortality (HR=0.78, 95% CI 0.39-1.57, p=0.50) compared to patients in highest quartiles, nor was one SD decrease in MCS score associated with the risk

of all-cause or cause-specific death (table 3). When combined categories of mood problems and lacunar infarcts were distinguished, patients with a combination of lowest quartile of MCS score, representing most severe mood problems, and lacunar infarcts were at strongly increased risk of all-cause mortality (HR=3.97, 95% CI 2.18-7.22) compared to patients in highest quartiles of MCS score and no lacunar infarcts (figure 1a).

Table 3 Cox proportional hazard models of the relationship between mood problems and death in patients with (n=209) and without lacunar infarcts (n=901)

			Hazard Ratio (95% CI)		
	No. of deaths	No. of person years	Model 1	Model 2	Model 3
Lacunar infarcts present (n=209)					
Mood problems					
Dichotomous (n=53)[£]					
All-cause death[‡]	18	258	2.72 (1.49 – 4.97)	2.75 (1.41 – 5.38)	2.66 (1.35 – 5.24)
Continuous (n=209)[†]					
All-cause death	47	1162	1.50 (1.11 – 2.02)	1.53 (1.10 – 2.13)	1.52 (1.09 – 2.11)
Vascular death	27	1162	1.36 (0.90 – 2.05)	1.60 (1.01 – 2.54)	1.65 (1.04 – 2.63)
Non-vascular death	20	1162	1.68 (1.07 – 2.63)	1.64 (1.00 – 2.69)	1.64 (0.99 – 2.74)
Lacunar infarcts absent (n=901)					
Mood problems					
Dichotomous (n=225)[£]					
All-cause death[‡]	10	1378	0.73 (0.37 – 1.44)	0.78 (0.39 – 1.57)	0.79 (0.39 – 1.58)
Continuous (n=901)[†]					
All-cause death	60	5445	0.88 (0.66 – 1.17)	0.94 (0.71 – 1.25)	0.96 (0.72 – 1.27)
Vascular death	25	5445	0.80 (0.53 – 1.21)	0.85 (0.55 – 1.33)	0.86 (0.55 – 1.35)
Non-vascular death	34	5445	0.93 (0.64 – 1.35)	1.02 (0.70 – 1.48)	1.04 (0.72 – 1.52)

CI, Confidence interval; SD, Standard deviation; MCS, Mental component summary; WML, White matter lesion; ICV, Intracranial volume

[£] Lowest quartile (<43.1) vs. three highest quartiles of MCS score

[†] Per SD decrease in MCS score

[‡] Because of the low number of events in different strata of lacunar infarcts, we only assessed associations of dichotomized MCS score with all-cause death

Model 1: adjusted for age and sex

Model 2: additionally adjusted for hypertension, diabetes mellitus, body mass index, smoking (pack-years), alcohol consumption, intima media thickness, physical functioning, antidepressant use and large infarcts on MRI

Model 3: additionally adjusted for total WML volume (% of ICV)

The association of mood problems with mortality was not modified by WML volume (mood problems dichotomous*WML p=0.72, mood problems continuous*WML p=0.48), therefore we did not repeat the analysis of mood problems and mortality in strata of WML volume. Cumulative hazard curves showed that the combined effect of lowest quartile of MCS score, representing most severe mood problems, and highest quartile of WML volume on all-cause

mortality (HR=2.40, 95% CI 1.30-4.43) was comparable to the sum of the individual effects of lowest quartile of MCS score and highest quartile of WML volume on all-cause mortality (figure 1b).

When number of lacunar infarcts was distinguished, adjustment for one lacunar infarct (n=95) and ≥2 lacunar infarcts (n=114) did not attenuate the effect estimates of the association of mood problems with all-cause mortality, or with vascular and non-vascular causes of death (data not shown). The presence of one lacunar infarct as well as ≥2 lacunar infarcts both modified the association of mood problems with mortality (mood problems dichotomous*one lacunar infarct p=0.02, mood problems continuous*one lacunar infarct p=0.02; mood problems dichotomous*≥2 lacunar infarcts p=0.02, mood problems continuous*≥2 lacunar infarcts p=0.14). The increase in the risk of all-cause mortality for patients in the lowest quartile of MCS score, compared to those in higher quartiles, was slightly larger in patients with one lacunar infarct (HR=3.14, 95% CI 1.28-7.69) than in those with ≥2 lacunar infarcts (HR=2.64, 95% CI 1.15-6.07) in model 1.

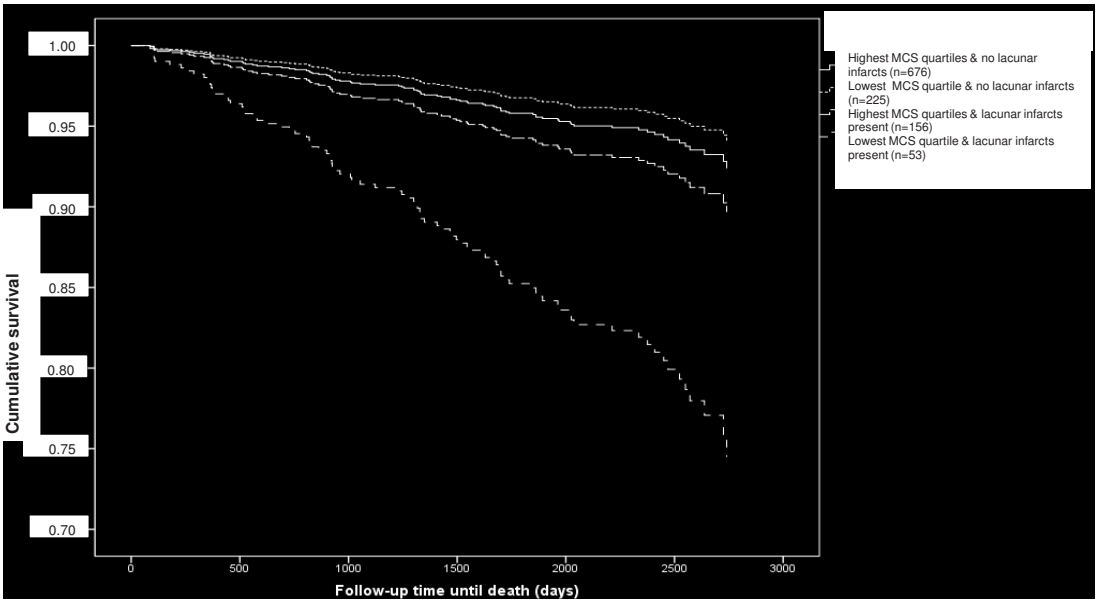

Figure 1a Cumulative hazard curve illustrating the cumulative survival (%) for combined categories of Mental Component Summary (MCS) score (lowest quartile vs. three highest quartiles) and lacunar infarcts (present vs. absent), adjusted for age, sex, hypertension, diabetes mellitus, body mass index, smoking (pack-years), alcohol consumption, intima media thickness, physical functioning, antidepressant use, large infarcts on MRI and white matter lesion volume.

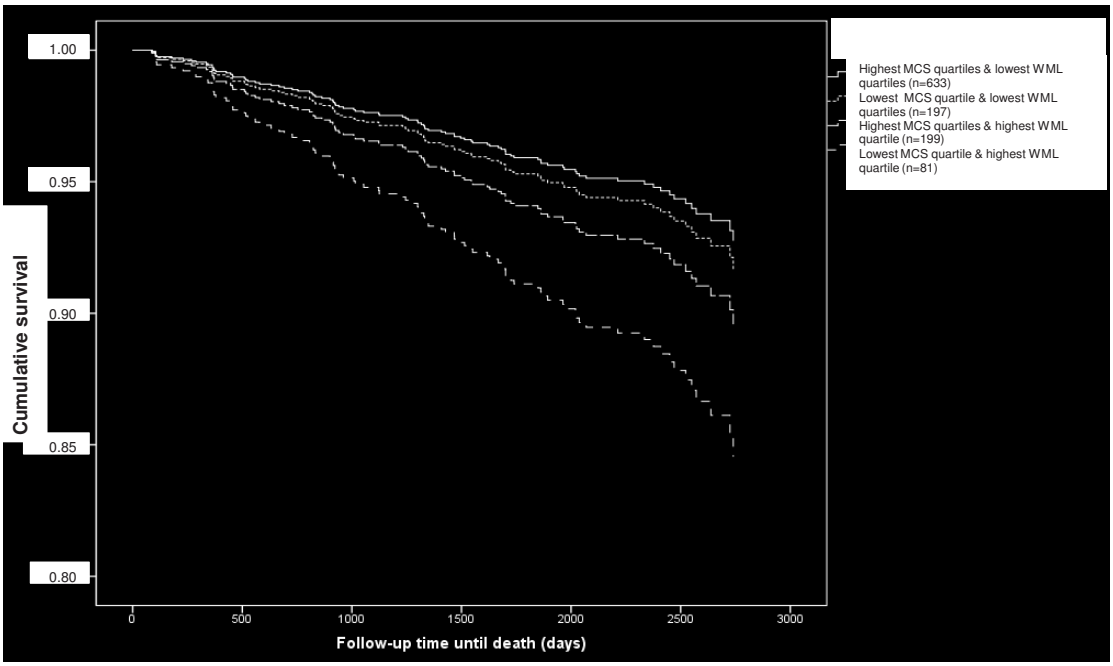

Figure 1b Cumulative hazard curve illustrating the cumulative survival (%) for combined categories of Mental Component Summary (MCS) score (lowest quartile vs. three highest quartiles) and white matter lesion (WML) volume (highest quartile vs. three lower quartiles), adjusted for age, sex, hypertension, diabetes mellitus, body mass index, smoking (pack-years), alcohol consumption, intima media thickness, physical functioning, antidepressant use and infarcts on MRI.

Discussion

In this cohort of patients with symptomatic atherosclerotic disease, mood problems strongly increased the risk of mortality in patients with lacunar infarcts but not in those without lacunar infarcts. This association was independent of age, sex, clinical and subclinical atherosclerosis, physical functioning, antidepressant use and concurrent MRI lesions.

Previous studies examining the association of depression with risk of mortality, investigated various potential underlying mechanisms by which depression may lead to an increased risk of mortality [14]. Despite the large number of candidate mechanisms, including antidepressant cardiotoxicity, vascular risk factors [10,11], nonadherence to cardiac prevention and treatment regimens [12,13], lower heart rate variability [7], increased platelet aggregation [8] and inflammatory processes [9], it remains unknown which of these, if any, can explain this relation [14].

To our knowledge, we are the first to investigate the role of CSVD in the relation between mood problems and mortality in patients with symptomatic atherosclerotic disease. Recently, we found that WML and lacunar infarcts increased risk of death in this population [21], and in the present study we observed that the combination of mood problems and lacunar infarcts

contributes to an even greater risk of death. Although the effect of lacunar infarcts on cognitive functioning has been found to increase with increasing number of lacunar infarcts [36,37], we found no such effect on the relation between mood problems and mortality. An interesting finding is that mood problems were associated with death from vascular as well as non-vascular cause. Our findings are in line with the existing literature that has associated post-stroke depression with increased mortality risks [4,5], in so far that we observed a relation between mood problems and mortality in patients with lacunar infarcts. Contrary to most studies that could not demonstrate an interaction effect between depressive symptoms and a history of stroke or cardiovascular disease [38,39], we observed that the combined effect of mood problems and lacunar infarcts on the risk of mortality was much greater than their additive effect.

One explanation for our findings could be that the greater overall vulnerability of patients with lacunar infarcts may lead to an increased effect of mood problems on adverse events. An alternative explanation may be that patients with lacunar infarcts suffer from a different type of mood problems that increase the risk of death. Although we did not formally assess depression, this finding would fit with the 'vascular depression' hypothesis. The 'vascular depression' hypothesis has proposed that disruption of frontal-subcortical pathways by small-vessel lesions can predispose to a subtype of depression [24,25] that is essentially different from non-vascular depression [26]. Not only is disruption of these pathways associated with a distinct clinical presentation [40,41], 'vascular depression' has also been associated with a significantly poorer clinical outcome, with weaker response to pharmacological treatment, more and longer hospitalizations, lower remission rates and more concomitant somatic disease than non-vascular depression [26]. Because we did not formally assess depression in this study, we could not determine to what extent the mood symptoms were characteristic of vascular depression.

Although lacunar infarcts and WML are often considered as different manifestations of a single underlying disease, i.e. cerebral small-vessel disease, our findings suggest a different role of lacunar infarcts and WML in the relation between mood problems and mortality. This is in line with our previous findings that lacunar infarcts but not WML volume are associated with the risk of depressive symptoms [42], and that lacunar infarcts and WML seem to be associated with a different prognosis in patients with symptomatic atherosclerotic disease [21].

Strengths of our study include the large number of patients included, the extensive information on cardiovascular risk factors and the extent of clinical and subclinical atherosclerosis, the stringent outcome monitoring, and the automated brain segmentation method. A limitation is that we did not use a standardized instrument to measure depression.

Although the MCS has been shown to be a good indicator of mood problems, the use of this scale may have contributed to a decreased contrast between patients with and without mood problems. However, this will most likely have resulted in a relative underestimation of the effect estimates. Also, the use of this scale will have resulted in assessment of more aspecific symptoms of mood problems than a formal depression assessment would have. Further, despite the large sample size we did not have enough power to distinguish the effect of different locations of lacunar infarcts and WML, including frontal-subcortical pathways. Finally, because our sample consisted of patients with symptomatic atherosclerotic disease, we do not know whether the findings can be generalized to the general population.

In sum, we found a much stronger effect of mood problems on the risk of death in patients with lacunar infarcts compared to those without lacunar infarcts. From our findings it cannot be concluded whether mood problems may be a cause or a consequence of lacunar infarcts, or whether both are caused by a common underlying mechanism. Nevertheless, our findings not only show that mood problems are associated with a worse prognosis in patients with symptomatic atherosclerotic disease, they also suggest that patients with the combination of lacunar infarcts and mood problems are at particularly high risk of vascular as well as non-vascular death. Patients with lacunar infarcts may be especially vulnerable to the effect of mood problems on poor outcome, and mood problems may therefore warrant extra close attention in these patients. Additional studies are needed to replicate our findings and to investigate whether our findings can be generalized to the general population.

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Chapter 3

Antidepressant use and cerebral small-vessel disease

Chapter 3.1

Antidepressant use is related to larger white matter lesion volume in patients with symptomatic atherosclerotic disease. The SMART-MR study

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Abstract

Objectives

Although a relation between depression and white matter lesions (WML) is frequently observed, the direction of causation remains unknown. We investigated whether depressed mood was associated with increased progression of WML volume during 4 years follow-up, and the relative contribution of mood symptoms and antidepressant use to this relation.

Methods

Within the SMART-MR study 594 patients (58±10 years) with symptomatic atherosclerotic disease had assessments of mood symptoms and antidepressant use and 1.5T MRI at baseline and after 3.9±0.4 years follow-up. Mood symptoms were assessed using the Mental Health Index (MHI-5). Depressed mood was defined as antidepressant use and/or MHI-5 score ≤52. Volumetric WML measures (deep and periventricular) were obtained with automated segmentation. Linear regression analyses were adjusted for age, sex, baseline WML volume, follow-up time, vascular risk factors and infarcts.

Results

Depressed mood was not associated with larger WML volume at baseline. However, when separate contributions were distinguished, antidepressant use was associated with greater deep (B=0.50mL, 95%CI 0.04 to 0.96) and periventricular WML volume (B=0.47mL, 95%CI 0.05 to 0.89) at baseline, while mood symptoms were not. Antidepressants were associated with a modest but non-significant increase in progression of periventricular WML volume over 4 years of follow-up (B=0.21mL, 95%CI -0.05 to 0.47).

Conclusions

Antidepressants, but not mood symptoms, were associated with greater WML volume in patients with symptomatic atherosclerotic disease. Future studies are needed to determine whether this may be a direct effect, or whether other underlying diseases for which antidepressants are prescribed influence this relation.

Introduction

Increasing evidence has shown that depression and cardiovascular disease not only commonly co-occur, but also influence each other [1]. Approximately 20% of patients recovering from myocardial infarction or stroke fulfil the criteria for depression [2,3], but also in patients with stable cardiovascular disease depression commonly occurs [1]. On the other hand, depression is a risk factor for future cardiovascular events and mortality both in the general population [4] and in patients with existing cardiovascular disease [2,5].

Despite the large number of candidate mechanisms investigated, the underlying mechanism linking depression and cardiovascular disease remains unclear [6]. One of the proposed mechanisms includes the presence of atherosclerotic damage to the cerebral small vasculature, characterized by white matter lesions (WML) on brain magnetic resonance imaging (MRI) [7]. WML are not only a common finding on brain MRI in patients with cardiovascular disease [8], but have also been identified as risk factor for recurrent vascular events and mortality [9]. On the other hand, significantly greater WML volumes have been found in depressed persons compared to healthy controls of similar age and sex [10]. According to the 'vascular depression' hypothesis [11,12], WML may predispose to depression due to impaired nerve conduction in brain regions involved in the regulation of emotions as a direct result of disruption of frontal-subcortical circuits.

Although various studies confirmed a cross-sectional relation between WML severity and depression [13,14], the direction of causation remains unclear. Most longitudinal studies investigated the influence of baseline WML severity on the development or change in depressive symptoms during one to four years follow-up, and reported highly diverse findings [15-19]. Although one study reported a relation between WML volume at baseline and an increased risk of incident depressive symptoms [15], two other studies reported an association of baseline WML severity with an increase or perseverance, but not incident, depressive symptoms during follow-up [16,17], whereas two others could not demonstrate any significant relationship [18,19]. Only one study on the other hand investigated the relation between WML and depressive symptoms in the opposite direction, suggesting that patients with depression at baseline, defined as lifetime major depressive episode or current antidepressant use, show an increased progression of WML volume [15]. It is however unclear to what extent the observed association may have been driven by antidepressant use, since only a composite definition of depression was used. A recent study suggested that antidepressant medication use may be an independent risk factor for progression of WML [20], but because a visual rating scale was used the estimation of WML progression was rather robust and may need replication.

The aim of our study was to examine whether depressed mood, defined as current mood symptoms or antidepressant use, was associated with larger WML volume at baseline and with more progression of WML volume during four years follow-up. In addition, we investigated the relative contributions of antidepressant medication intake and mood symptoms to this association.

Materials and methods

Participants

Data were used from the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study investigating brain changes on MRI in independently living patients with different manifestations of arterial disease. Methods for baseline examinations were described previously [21]. In brief, between May 2001 and December 2005, 1309 patients were included who were newly referred to the University Medical Center Utrecht with coronary artery disease, cerebrovascular disease, peripheral disease or abdominal aortic aneurysm, and who had no MRI contraindications. During a 1-day visit to our medical center, physical examination, ultrasonography of the carotid arteries, and blood and urine sampling were performed. Risk factors and medical history were assessed with questionnaires. Assessment of mood problems was added to these questionnaires in January 2002. For the current study, data were used from 1110 patients with available data on MRI and mood symptoms.

Between January 2006 and May 2009, all participants still alive were invited for follow-up measurements, including MRI of the brain, neuropsychological testing, physical examination and blood and urine sampling. The SMART-MR study was approved by the ethics committee of our institution and written informed consent was obtained from all participants. In total, 643 of the surviving cohort (61% of n=1052) gave written informed consent; 394 (36%) persons refused, and 15 (1%) were lost to follow-up.

Magnetic resonance imaging protocol

MRI investigations were performed on a 1.5-Tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE): 235/2 ms; flip angle, 80º), a transversal T2-weighted turbo spin-echo sequence (TR/TE: 2200/11 ms and 2200/100 ms; turbo factor 12), a transversal T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI): 6000/100/2000 ms) and a transversal inversion recovery (IR) sequence (TR/TE/TI: 2900/22/410 ms) (field of view 230x230 mm; matrix size, 180x256; slice thickness, 4.0 mm; no gap; 38 slices).

Brain segmentation

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique was described elsewhere [22,23]. The segmentation program distinguishes cortical gray matter, white matter, sulcal and ventricular cerebrospinal fluid (CSF), and lesions. The results of the segmentation analysis were visually checked for presence of infarcts and adapted if necessary to make a distinction between WML and infarct volumes. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, the volumes of WML and infarcts. All volumes cranial to the foramen magnum were included. Total intracranial volume (ICV) was calculated by summing the total brain volume and volumes of the sulcal and ventricular CSF.

Infarcts and white matter lesions

The whole brain was visually searched for infarcts by a trained investigator and a neuroradiologist. Raters were blinded to patient history and diagnosis. Discrepancies in rating were re-evaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images in order to distinguish them from WML. Dilated perivascular spaces were distinguished from infarcts based on their location (along perforating or medullary arteries, often symmetric bilaterally, usually in the lower third of the basal ganglia or centrum semiovale), form (round/oval), and absence of gliosis. Brain infarcts were categorized as cortical-, lacunar-, large subcortical-, large basal ganglia-, infratentorial, and small brainstem infarcts. Periventricular WML were defined as WML adjacent to or within 1 cm of the lateral ventricles in both hemispheres. Deep WML were located in deep white matter tracts and may or may not have adjoined periventricular lesions. Volumes of periventricular and deep WML were summed to obtain total volume of WML.

Assessment of depressed mood

Mood symptoms were assessed at baseline with the five-item Mental Health Index (MHI-5), a subscale of the Short-Form 36 Medical Outcomes Study Health Survey [24]. Patients were asked how much of the time over the past month (all, most, good bit, some, little, or none) they: 1) felt nervous; 2) felt downhearted and blue; 3) felt calm and peaceful; 4) felt so down that nothing could cheer them up; 5) felt happy. Scores are transformed into a variable ranging from 0-100, with lower scores indicating more mood symptoms. The MHI-5 performs well in screening for depression [25,26]. In accordance with previous recommendations, a cut-off score ≤52 was used to define the presence of mood symptoms [27,28].

Antidepressant use (selective serontonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors or others) was assessed via questionnaires at baseline and follow-up. Depressed mood was defined as having either mood symptoms (MHI-5 score ≤52) or taking antidepressants [28,29].

Other variables

During the visit to the medical center, an overnight fasting venous blood sample was taken to determine glucose levels. Height and weight were measured and the body mass index (BMI) was calculated (kg/m^2). Systolic and diastolic blood pressures (mm Hg) were measured twice and averaged. Hypertension was defined as mean systolic blood pressure ≥160 mm Hg, mean diastolic blood pressure ≥95 mm Hg or self reported antihypertensive drug use. Diabetes mellitus was defined as glucose ≥7.0 mmol/L or self reported use of oral antidiabetic drugs or insulin. Hyperlipidemia was defined as total cholesterol >5.0 mmol/L, low-density lipoprotein cholesterol >3.2 mmol/L or self reported use of lipid lowering drugs. Smoking habits and alcohol intake were assessed with questionnaires. Pack-years of smoking was calculated; alcohol intake was categorized into never, former, or current. As a measure of the severity of subclinical atherosclerosis, ultrasonography was performed to measure the intima-media thickness (IMT) (mm) in the left and right common carotid arteries, represented by the mean value of six measurements.

Study sample

Of the 643 patients participating at follow-up, MRI variables at follow-up were missing in 49 patients (no MRI (n=37), or artefacts (n=12)), resulting in a total sample of 594 patients.

Data analysis

We used multiple imputation [30] (10 datasets) to address missing values in the study sample of 594 patients, using the statistical programme R (AregImpute). Data were analyzed using PASW version 17.0 (Chicago, III, USA), by pooling the 10 imputed datasets. First, baseline characteristics were compared between patients with and without depressed mood. Then, linear regression analysis was used to investigate the cross-sectional association of depressed mood (as independent variable) with WML volume (as dependent variable) at baseline. WML volume was natural log-transformed (ln) to obtain a normal distribution. Next, we investigated the prospective association of depressed mood at baseline (as independent variable) with change in ln WML volume during follow-up. Ln WML volume at follow-up was entered as dependent variable, and adjustments were made for age, sex, ln WML volume at baseline, follow-up time and intracranial volume (model 1), and additionally for smoking, alcohol use, BMI, hypertension, diabetes mellitus, hyperlipidemia, IMT and infarcts on MRI (model 2).

Second, we repeated the analysis distinguishing deep and periventricular WML volumes to examine whether the strength of the relation between depressed mood and WML volume was influenced by the location of WML. Third, to explore the relative contribution of these variables in the associations, we repeated all analyses with antidepressant use and MHI-5 score ≤52 as separate variables in the same model. Because previous studies suggested a different effect of SSRI and TCA use on WML volume and clinical prognosis [20,28], we also examined the relative contribution of SSRI and TCA use separately.

Table 1 Baseline characteristics of the total sample and according to depressed mood status

	Total sample (n=594)	Depressed mood* (n=114)	No depressed mood* (n=480)
Age (years)†	58 ± 9.5	56 ± 8.9	58 ± 9.7
Female sex (%)	20	34	17
BMI (kg/m²)†	27 ± 3.6	28 ± 3.9	27 ± 3.4
Smoking (pack-years)‡	20 (0-49)	25 (0-55)	19 (0-46)
Alcohol use			
- Never	15	20	14
- Former	8	13	6
- Current	78	67	80
Hypertension (%)	50	51	50
Diabetes mellitus (%)	16	16	16
Hyperlipidemia (%)	75	74	79
IMT (mm)†	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
Total intracranial volume (mL)†	1462 ± 128	1446 ± 125	1466 ± 129
Absolute WML volume (mL)‡	1.3 (0.4-6.4)	1.3 (0.5-6.4)	1.3 (0.4-6.5)
- Deep	0.6 (0.1-3.2)	0.6 (0.2-3.5)	0.6 (0.1-3.1)
- Periventricular	0.7 (0.2-3.6)	0.7 (0.1-2.9)	0.7 (0.2-4.0)
Cerebral infarct (%)	25	24	25
Antidepressant use (%)	5	25	0
- SSRI	2	12	0
- TCA	2	10	0
- Other	1	5	0
Overall MHI-5 score‡	76 (50-92)	48 (32-74)	80 (64-96)
- MHI-5 score ≤52 (%)	16	82	0

BMI, Body mass index; IMT, Intima media thickness; WML, White matter lesion; SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressant; MHI-5, 5-item Mental Health Index

* Depressed mood defined as MHI-5 score ≤52 or antidepressant use

† Mean ± SD; ‡ Median, (10^{th}-90^{th} percentile)

Percentage of missing values: intracranial volume and WML volumes: 2.9%, MHI-5: 2.7%, IMT: 2.2%, diabetes: 1.5%, hypertension and hyperlipidemia: 0.7%, alcohol use: 0.5%, all other variables: 0.0 %

Results

The mean age of the study population was 58±9.5 years and 80% was male (table 1). Compared to those without, patients with depressed mood were more often female (34% vs. 17%), with greater BMI (mean, 28 vs. 27 kg/m^2), more pack-years of smoking (median, 25 vs. 19), less current alcohol use (67% vs. 80%) and lower MHI-5 score (median, 48 vs. 80). Mean follow-up was 3.9±0.4 years.

Depressed mood and WML volume at baseline

Depressed mood was not significantly associated with total WML volume at baseline (table 2). Also when deep and periventricular WML volumes were distinguished, no significant associations of depressed mood with WML volume were found (table 2).

Table 2 Cross-sectional associations at baseline of depressed mood as independent variable, and white matter lesion volumes as dependent variable (n=594)

	Log-transformed white matter lesion volume					
	Total		**Deep**		**Periventricular**	
	B	**95% CI**	**B**	**95% CI**	**B**	**95% CI**
Depressed mood*						
Model 1	0.08	(-0.14 to 0.29)	-0.13	(-0.13 to 0.38)	-0.04	(-0.27 to 0.20)
Model 2	0.07	(-0.15 to 0.29)	-0.12	(-0.14 to 0.38)	-0.04	(-0.27 to 0.19)
Antidepressant use						
Model 1‡	0.65	(0.26 to 1.04)	0.57	(0.11 to 1.03)	0.56	(0.14 to 0.98)
Model 2	0.57	(0.18 to 0.95)	0.50	(0.04 to 0.96)	0.47	(0.05 to 0.89)
MHI-5 score ≤52						
Model 1†	-0.07	(-0.31 to 0.16)	-0.03	(-0.24 to 0.31)	-0.19	(-0.44 to 0.06)
Model 2	-0.07	(-0.30 to 0.16)	-0.04	(-0.24 to 0.31)	-0.17	(-0.42 to 0.08)

WML, White matter lesion; CI, Confidence interval; MRI; Magnetic resonance imaging

* Depressed mood defined as MHI-5 score ≤52 or antidepressant use

Model 1 Adjusted for age, sex and intracranial volume

Model 2 Additionally adjusted for smoking, alcohol use, hypertension, diabetes mellitus, hyperlipidemia, intima media thickness and infarcts on MRI

† Additionally adjusted for MHI-5 score ≤52, and vice versa

When we examined the independent influence of MHI-5 score ≤52 and antidepressant use on WML volume, the use of any antidepressant was significantly associated with greater total WML volume (B=0.65mL, 95% CI 0.26 to 1.04). Additional adjustment for covariates did not attenuate this effect (table 2). When deep and periventricular WML volumes were distinguished, antidepressant use was significantly associated with greater deep and

periventricular WML volume (table 2; figure 1). When the type of antidepressant medication was distinguished, both SSRI (B=0.43mL, 95% CI -0.24 to 1.11) and TCA use (B=0.47mL, 95% CI -0.27 to 1.20) contributed to the association with deep WML volume; the association with periventricular WML use was primarily driven by SSRI (B=0.65mL, 95% CI 0.04 to 1.26) and not by TCA use (B=0.01mL, 95% CI -0.66 to 0.68).

No significant associations of mood symptoms as indicated by MHI-5 score ≤52 with total or regional WML volumes were found (table 2).

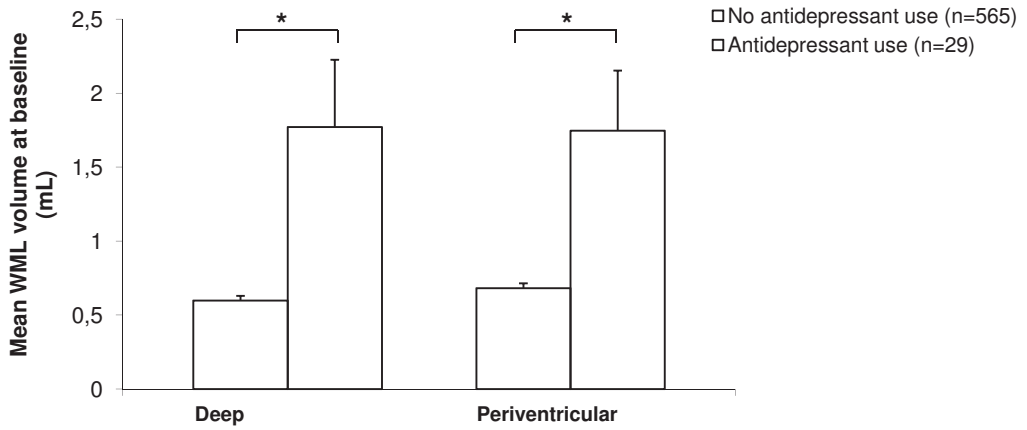

Figure 1 Mean deep and periventricular white matter lesion (WML) volumes (mL) at baseline for patients with and without antidepressant medication use, adjusted for age, sex and intracranial volume. Error bars indicate standard errors; statistically significant differences are indicated with an asterix (p-value=0.01).

Depressed mood and change in WML volume

Depressed mood was not significantly associated with a change in total WML volume during follow-up (B=-0.06mL, 95% CI -0.21 to 0.10). Also when deep and periventricular WML volumes were distinguished, no significant associations of depressed mood with WML volume were found (data not shown).

When we examined the independent influence of MHI-5 score ≤52 and antidepressant use on WML progression, the use of any antidepressant was not associated with a greater change in total WML volume (B=0.07mL, 95% CI -0.21 to 0.35). When deep and periventricular volumes were distinguished, antidepressant use was associated with a modest but non-significant greater increase in periventricular WML volume (figure 2; fully adjusted: B=0.21, 95% CI -0.05 to 0.47), but not deep WML volume (B=-0.11, 95% CI -0.47 to 0.25). When the type of antidepressant medication was distinguished, similar trends towards an increased progression of periventricular WML volume were seen (figure 3).

No significant associations of mood symptoms as indicated by MHI-5 score ≤52 with change in total WML volume B=-0.07, 95% CI -0.23 to 0.09) or regional WML volumes were found (data not shown).

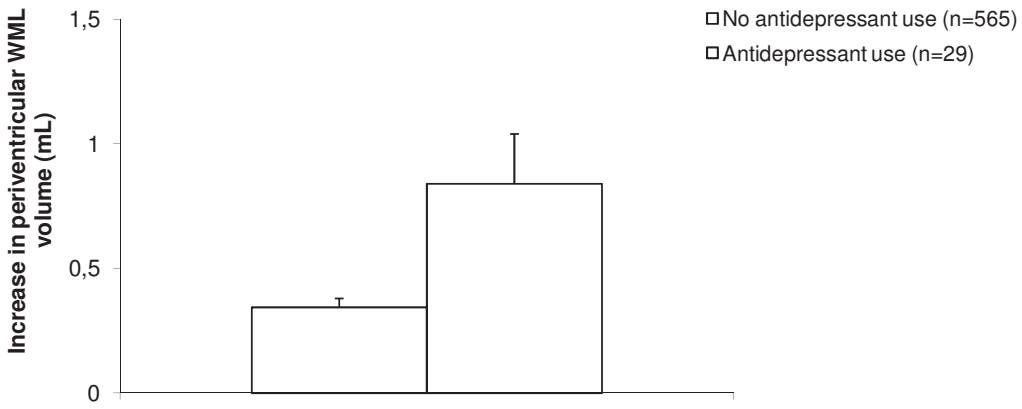

Figure 2 Mean increase in periventricular white matter lesion (WML) volume (mL) during follow-up for patients with and without any antidepressant medication use, adjusted for age, sex, intracranial volume and follow-up time. WML volumes and standard errors are back transformed from the natural log transformation. Error bars indicate standard errors.

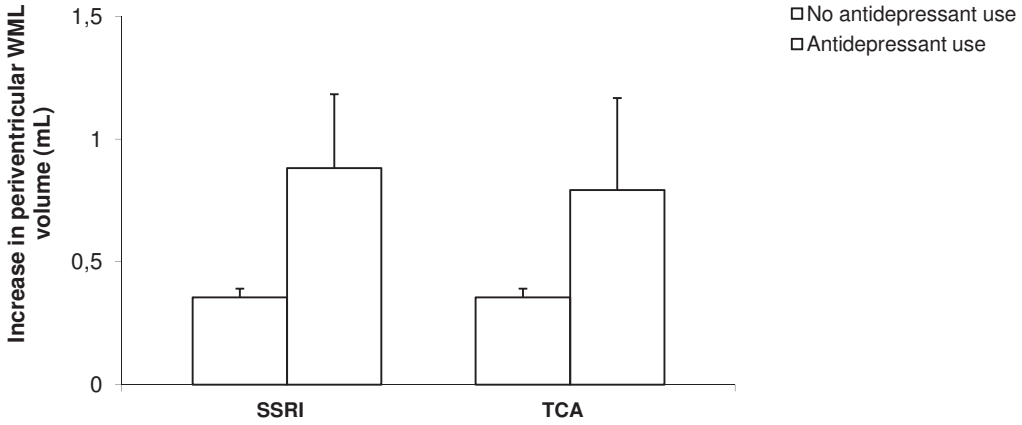

Figure 3 Mean increase in periventricular white matter lesion (WML) volume (mL) during follow-up for patients with and without Selective Serotonin Reuptake Inhibitor (SSRI) and Tricyclic Antidepressant (TCA) use, adjusted for age, sex, intracranial volume and follow-up time. WML volumes and standard errors are back transformed from the natural log transformation. Error bars indicate standard errors.

Discussion

In a cohort of patients with symptomatic atherosclerotic disease, we observed that antidepressant use was associated with increased deep and periventricular WML volumes at baseline, whereas mood symptoms were not. In addition, antidepressants were associated with a modest but non-significant increase in progression of periventricular WML volume during four years follow-up.

Before we interpret our findings, several strengths and limitations have to be considered. Strengths of our study include the prospective design; the large sample size; the automated segmentation technique used to obtain volumetric measures of WML which provides more precise and objective estimates than visual rating scales [31] and enabled accurate measurement of small volume changes over time [32]; and the extensive information on cardiovascular risk factors and subclinical atherosclerosis, for which we could adjust in our analyses. A limitation is that we did not have a formal diagnosis of major depressive disorder, although we tried to define a clinically relevant group by combining high mood symptom scores and antidepressant use. Another limitation is that information on antidepressant use was acquired through self-report questionnaires rather than using data from physician or pharmacy registries, and that we did not have information on the indication, duration and dose of antidepressant use while this may be relevant for the clinical prognosis [33].

Although a cross-sectional relation between depressive symptoms and WML volume has frequently been observed [13,14], we did not find an association of depressed mood, defined as MHI-5 score ≤52 or antidepressant use, with greater WML volume. Also, when we examined the relative contribution of mood symptoms and antidepressant use, we did not find an association of mood symptoms with greater WML volume. A possible explanation for this finding may be that the MHI-5 does not assess motivational symptoms, whereas other depression screening instruments assess both mood and motivational symptoms. According to the 'vascular depression' hypothesis, WML may predispose to or perpetuate depression as a result of the disruption of frontal-subcortical circuits [11,12]. Because frontal-subcortical dysfunction is primarily characterized by the presence of motivational symptoms [34], these symptoms are thought to be dominant in persons with WML-related depression.

Antidepressant use, however, was associated with larger WML volume in our study. One explanation for this relation is that the use of antidepressants reflects the severity of depression. However, along with another study [20] we observed that the relation between antidepressant use and WML volume was independent of the presence of mood symptoms at baseline. Further, another study found that the relation between depression and stroke was primarily explained by antidepressant use and not by depressive symptoms, which also

contradicts the hypothesis that antidepressant use simply is a marker for the severity of depression [28].

Alternatively, one could hypothesize that a greater WML volume may be a direct result of these antidepressant drug types. SSRI as well as TCA use have been previously identified as independent risk factors for cardiovascular disease, including coronary artery disease and stroke [28,29,33,35-38]. It has been suggested that SSRI use may predispose to WMLs through antidepressant-induced vasoconstriction, which is mediated by serotonin receptors on smooth muscle cells, prompting thromboembolic events in atherosclerotic cerebral arteries [33]. In addition, TCAs have been associated with various cardiovascular effects, including increased heart rate and orthostatic hypotension [20], which may predispose to decreased cerebral perfusion.

Yet another explanation may be that antidepressants were prescribed for complaints related to or resulting from white matter lesions. At older age, antidepressants are also often prescribed for conditions other than depression, including headache, anxiety and sleeping problems [38]. Because we did not have information on the indication for antidepressant treatment, it is possible that the observed relation between antidepressants and WML volume may not reflect an association with depression but with another underlying disease. A speculative alternative hypothesis to explain our findings is that antidepressants were prescribed for persons with depressive or memory complaints related to mild cognitive impairment or preclinical dementia. Previous studies have associated an increased severity and progression of periventricular WML volume, and to a lesser extent deep WML volume, with mild cognitive impairment and cognitive decline [39-43]. Mild cognitive impairment can lead to memory complaints and depressive symptoms, and these complaints may have been an indication for prescribing antidepressants.

The 'vascular depression' hypothesis states that WML may predispose to or perpetuate depression and as such, the direction of causality is that depression results from WML. However, because cardiovascular disease can also lead to depression, it has also been hypothesized that depression increases the risk for WML [15]. Because studies that investigated the prospective relationship between clinically relevant depressive symptoms and WML severity yielded highly inconsistent findings [15-19], it remains unclear whether WML is a cause of depressive symptoms, a consequence, or whether both may result from a mutual underlying mechanism. So far, only one other population-based study investigated whether depression at baseline, defined as lifetime major depressive episode or current antidepressant use, was associated with increased progression of WML volume during four years follow-up [15]. Although the authors found depression to be associated with an

increased progression of total WML volume, it is unclear to what extent this association may have been driven by a lifetime diagnosis of depression or by underlying antidepressant use because these were not examined separately. The one population-based study that examined the direct relation between antidepressant use and progression of WML volume, found SSRI as well as TCA use to be associated with an increase in WML severity during five years follow-up [20]. In that study, participants brought medication containers to the clinic and total WML severity was estimated using a visual rating scale. Although we also found that SSRI and TCA use were associated with modest increase in progression of periventricular WML volume during four years follow-up, this difference was not statistically significant, possibly due to the small number of patients using antidepressants.

In conclusion, we found that antidepressants, but not mood symptoms, were associated with larger WML volumes in patients with symptomatic atherosclerotic disease. Future studies linking pharmacy registry information and clinical data to provide detailed information on the dose, duration and prescription indication of antidepressants are, however, needed to determine whether increased WML volume may be a direct cause of antidepressant use, or whether it may be explained by another underlying disease which may have been an indication for prescribing antidepressants.

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Chapter 4

Location of cerebrovascular disease, depression and cognition

Chapter 4.1

Location of cerebrovascular and degenerative changes, depressive symptoms and cognitive functioning in later life. The SMART-Medea study

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Abstract

Objectives

Depression and cognitive impairment are highly prevalent in later life, and frequently co-occur. Structural changes in critical brain regions may underlie both conditions. We examined associations of infarcts, white matter lesions (WML) and atrophy at different locations with depressive symptoms and cognitive functioning.

Methods

Within the Second Manifestations of ARTerial disease-Memory, depression and aging (SMART-Medea) study, cross-sectional analyses were performed in 585 non-demented patients aged ≥50 years with symptomatic atherosclerotic disease. Volumetric measures of WML and atrophy were obtained with 1.5T MRI; infarcts were rated visually. Depressive symptoms were assessed with Patient Health Questionnaire-9 (score ≥6). Z-scores of executive functioning, memory and processing speed were calculated. Analyses were adjusted for age, sex, education, intelligence, vascular disease, physical functioning and co-occurrent brain changes.

Results

Depressive symptoms were present in 102 (17%) patients and were associated with poorer memory (B=-0.26, 95% CI -0.47 to -0.06). Large subcortical infarcts and lacunar infarcts in deep white matter tracts were both associated with depressive symptoms (RR=2.66, 95% CI 1.28-5.54; RR=2.02, 95% CI 1.14-3.59) and poorer executive functioning and memory. Periventricular WML volume was associated with poorer executive functioning; cortical infarcts in the left hemisphere and media flow region, ventricular volume and cortical atrophy were associated with slowed processing speed.

Conclusions

In this sample of non-demented elderly, subcortical infarcts contributed to an increased risk of depressive symptoms as well as cognitive impairment. This depended on location in projecting white matter tracts and not on infarct size.

Introduction

Depressive disorders and cognitive impairment are common and disabling conditions in the elderly. Moreover, depressive symptoms are frequently accompanied by impairment in several cognitive domains [1], which often persists after recovery from a depressive episode [2]. The mechanisms underlying this association are not fully understood, but structural cerebral changes, including atrophy and cerebrovascular changes, may contribute to depression as well as cognitive impairment in later life.

Location of structural changes in brain regions, involved in the regulation of emotions and cognitive functioning, has received increasing interest as an underlying mechanism in depressive symptoms and cognitive impairment. The 'vascular depression' hypothesis has proposed that disruption of frontal-subcortical pathways by small-vessel lesions could predispose to increased vulnerability of late-life depression [3] and was based on previous studies associating disruption of frontostriatal pathways with impairment in cognitive and behavioural functions [4]. Most neuroradiological studies investigating associations of infarcts, small-vessel lesions or atrophy with depressive symptoms or cognitive functioning however only assessed lesion severity, and did not examine the influence of lesion location [5-14]. Studies that did, often relied upon small sample sizes [15] or limited their investigations to infarcts, white matter lesions (WML) or atrophy alone [16-18]. Also, findings are highly diverse, with some studies emphasizing the importance of deep WML and lacunar infarcts in basal ganglia on the risk of depressive symptoms [17,18], and of periventricular WML and lacunar infarcts in the thalamus in predicting poorer cognitive functioning [14,16,19]. Others reported contradictory findings [20,21] or no significant associations [22]. Further, distinct cognitive domains were often not distinguished [15]. Finally, combining different study results is complicated by the heterogeneity in population characteristics and lesion rating methods. It would therefore be interesting to examine different lesion types and locations, depressive symptoms and cognitive functioning within one study population.

We examined the extent and location of large- and small-vessel infarcts, WML volume and atrophy, depressive symptoms and functioning in different cognitive domains in patients with symptomatic atherosclerotic disease. We expect that as a result of their vascular burden, these patients are more vulnerable for the presence of cerebrovascular and degenerative changes than the general population. We hypothesized that cerebrovascular lesions in frontal-subcortical pathways would be associated with an increased risk of depressive symptoms and poorer executive functioning, whereas cerebrovascular or atrophic changes in the left hemisphere and parietotemporal regions or thalamus would be associated with poorer memory and processing speed.

Methods

Subjects

The Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study is a prospective cohort study aimed to investigate brain changes on MRI in 1309 independently living patients with symptomatic atherosclerotic disease [23]. In brief, between May 2001 and December 2005, all patients newly referred to the University Medical Center Utrecht with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease or an abdominal aortic aneurysm (AAA), and without MR contraindications were invited to participate. Exclusion criteria were: age ≥80 years at inclusion, diagnosis of a terminal malignancy, not being independent in daily activities (Rankin scale >3), not being sufficiently fluent in Dutch, or being referred back to the referring specialist after one visit. During a 1-day visit to our medical center, physical examination, ultrasonography of the carotid arteries, blood and urine sampling and MRI of the brain were performed. Risk factors, medical history, and functioning were assessed with questionnaires. Neuropsychological testing was introduced in the SMART-MR study in January 2003 and was performed on the same day as the MRI and other investigations.

Between January 2006 and May 2009, all participants still alive were invited for follow-up measurements, including MRI of the brain, neuropsychological testing, physical examination, blood and urine sampling, risk factors, medical history, and functioning. In addition, as part of the SMART-Medea (Memory, depression and aging) study, an ancillary study to the SMART-MR study, aimed to investigate brain changes, psychosocial vulnerability and stress factors, depression measurements were added from March 2006. The SMART-MR and SMART-Medea study were approved by the ethics committee of our institution and written informed consent was obtained from all participants. In total, 754 of the surviving SMART-MR cohort (61% of n=1238) gave written informed consent and participated at follow-up; 466 persons (38%) refused or did not respond, and 18 persons (1%) were lost to follow-up.

Magnetic Resonance Imaging Protocol

MR investigations were performed on a 1.5-Tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE): 235/2 ms), a transversal T2-weighted turbo spin-echo sequence (TR/TE: 2200/11 ms and 2200/100 ms), a transversal T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI): 6000/100/2000 ms) and a transversal inversion recovery (IR) sequence (TR/TE/TI: 2900/22/410 ms) (field of view 230x230 mm; matrix size, 180x256; slice thickness, 4.0 mm; no slice gap; 38 slices).

Brain segmentation

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation [24,25]. The segmentation program distinguishes cortical gray matter, white matter, sulcal and ventricular cerebrospinal fluid (CSF), and lesions. Results of the segmentation analysis were visually checked for the presence of infarcts and adapted if necessary to make a distinction between WML and infarct volumes. Total brain volume was calculated by summing gray and white matter volumes and, if present, WML and infarct volumes. All volumes cranial to the foramen magnum were included. As a result, the total brain volume includes the cerebrum, brainstem and cerebellum. Total intracranial volume (ICV) was calculated by summing total brain volume and sulcal and ventricular CSF volumes.

Infarcts and white matter lesions

The whole brain was visually searched for infarcts by a trained investigator and a neuroradiologist. Raters were blinded to patient history and diagnosis. Discrepancies in rating were re-evaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images in order to distinguish them from WML. Dilated perivascular spaces were distinguished from infarcts based on their location (along perforating or medullary arteries, often symmetric bilaterally, usually in the lower third of the basal ganglia or centrum semiovale), form (round/oval), and absence of gliosis. Location, flow territory and type were scored for every infarct. Brain infarcts were categorized as cortical infarcts, lacunar infarcts, large subcortical infarcts and infratentorial infarcts. Large subcortical infarcts were sized >15 mm and were not confluent with cortical infarcts. Cortical and large subcortical infarcts were scored in the following locations: left and right hemisphere; anterior, media and posterior flow regions. We defined lacunar infarcts as infarcts of 3-15 mm in diameter and located in the frontal, parietal, temporal and occipital lobe, corona radiata, internal capsule, semioval center, thalamus or basal ganglia. Infratentorial infarcts were located in the brainstem or cerebellum.

Periventricular lesions were defined as WML adjacent to or within 1 cm of the lateral ventricles. Deep lesions were located in deep white matter tracts with or without adjoined periventricular lesions. Volumes of periventricular and deep WML were summed to obtain total WML volume. Volumes of WML were normalized for ICV, and expressed as percentage of ICV.

Brain volumes

All brain volumes (total brain volume, ventricular volume and cortical gray matter volume) were expressed relative to ICV. Brain parenchymal fraction (BPF) was used as an indicator for global brain atrophy, and cortical gray matter fraction for cortical brain atrophy.

Depressive symptoms

Depressive symptoms in the past two weeks were measured with the Patient Health Questionnaire-9 (PHQ-9) [26], which assesses the presence of the nine DSM-IV criteria for major depressive disorder on a 4-point scale (total score range 0-27). We used a cut-off score ≥6 to define presence of depressive symptoms because two recent studies, one of which was performed in patients with coronary heart disease, showed good performance using this cut-off score (sensitivity 82-83%, specificity 79-82%) in screening for a depressive episode [27,28].

History of depressive episodes was based on affirmative answers to one of the two DSM-IV core symptoms on the lifetime depression section in the questionnaire (ever having experienced depressed mood or loss of interest for at least 14 consecutive days), and the age of first depressive episode was assessed. Participants who experienced their first episode at 50 years or older were classified as having a first depressive episode in later life. This cut-off was chosen because of the relatively young age of our sample and because this cut-off was proven appropriate in detecting differences between age of onset groups in a previous study [29].

Neuropsychological assessment

We assessed memory, executive functioning, and processing speed and attention. For each of these three cognitive domains composite z-scores were computed by averaging z-scores of all subtests per domain.

Verbal memory was assessed with 5 consecutive trials of the 15-word learning test (a modification of the Rey Auditory Verbal Learning test) [30]. Immediate and delayed recall were assessed. Non-verbal memory was assessed with the delayed recall of the Rey-Osterrieth Complex Figure test [31].

Executive functioning was assessed with three tests. The visual elevator test (subtest of the Test of Everyday Attention [32]) is a timed test of 10 trials that measures mental flexibility and shifting of attention. The Brixton Spatial Anticipation test [33] was used to assess the capacity to discover logical rules and mental inhibition and flexibility. The total number of errors made was scored. The Verbal Fluency test (letter A, one minute time frame) was used to assess mental flexibility and employment of strategies. Before calculating the z-scores, the scores of the Visual Elevator test and Brixton Spatial Anticipation test were multiplied by minus one, so that lower scores represented poorer performance.

Attention was measured with the Digit Span Forward and Digit Span Backward. In total, there were 16 trials and the maximum of correct trials was scored. The Symbol substitution

test (subtest from the Wechsler Adult Intelligence Scale) was administered to measure processing speed, and the number of correct responses during a two minute time frame was scored. Global cognitive functioning was measured with the Mini-Mental State Examination (MMSE) [34]. Participants with a MMSE score <27 were examined by a physician who conducted an additional in-house standardized dementia interview and physical examination. The results of these investigations together with the outcome of the neuropsychological testing were discussed in a consensus meeting with a geriatrician to diagnose dementia.
Educational level was divided into eight categories, graded from primary school to academic degree, according to the Dutch educational system. Intelligence was assessed using the validated Dutch Adult Reading Test (DART) [35].

Other variables

During the visit to the medical center, an overnight fasting venous blood sample was taken to determine glucose levels. Systolic and diastolic blood pressures (mm Hg) were measured three times with a sphygmomanometer and averaged. Hypertension was defined as mean systolic blood pressure ≥160 mm Hg, mean diastolic blood pressure ≥95 mm Hg or self reported antihypertensive drug use. Diabetes mellitus was defined as history of diabetes mellitus, glucose ≥7.0 mmol/L or self reported use of oral antidiabetic drugs or insulin. Physical functioning was assessed with the Physical Component Summary scale of the Short Form-12 (SF-12) [36], a shortened version of the Short Form-36 (SF-36) Medical Outcomes Study Health Survey [37].

Study sample

Of the 754 patients initially included in the follow-up study, we selected all patients aged 50 years or older (n=680). Of these, 4 had dementia and were excluded. Of the remaining patients, data on MRI variables were missing in 56 patients (no MRI: 40, motion or artefacts: 16). Of these, data on the PHQ-9 questionnaire were missing in 6 patients, and cognition data were missing in 29 patients (no cognition tests due to logistical problems: 10, incomplete test data due to severe cognitive or behavioural impairment, or extreme visual or hearing handicaps: 19). This resulted in an analytical sample of 585 patients.

Data analysis

Depressive symptoms

Log-binomial and Poisson regression models with robust standard errors were used to investigate cross-sectional relationships between presence and location of infarcts, WML volume and atrophy as independent variables and presence of depressive symptoms as dependent variable. We estimated relative risks and accompanying confidence intervals (CI) [38] rather than odds ratios which overestimate the relative risk, particularly for outcomes that

are common (>10%) [39]. WML volume (% of ICV) and atrophy were entered per SD increase. In model I, associations were adjusted for age, sex and education. We additionally adjusted for hypertension, diabetes mellitus and physical functioning in model II. Because of possible inter-correlation of MRI variables, we additionally adjusted for co-occurrent infarcts and WML in model III. Because brain changes are thought to particularly increase the risk of first onset of depressive symptoms in later life, we repeated all analyses excluding patients with history of a depressive episode before age 50.

Cognitive functioning

Linear regression analysis was used to estimate cross-sectional associations of depressive symptoms (PHQ-9 score ≥6) with z-scores of executive functioning, memory and processing speed, because z-scores were continuous outcomes and assumptions for linear regression were not violated. Associations were adjusted for age, sex, DART score and education in model I. We additionally adjusted for hypertension, diabetes mellitus and physical functioning in model II.

Next, we estimated cross-sectional associations of presence and location of infarcts, WML volume and atrophy with z-scores of executive functioning, memory and processing speed in a similar way. We additionally adjusted for co-occurrent infarcts and WML in model III. We chose not to correct for multiple comparisons [40].

Results

Of the 585 patients included, 102 (17%) had a PHQ-9 score ≥6 (table 1). In total, 117 patients (20%) were included in the SMART-MR study at baseline with cerebrovascular disease.

Depressive symptoms

Before distinguishing location, only large subcortical infarcts increased the risk of depressive symptoms (table 2). All subcortical infarcts were located medially, of which five were located in the right, and two in the left hemisphere.

Lacunar infarcts located in the corona radiata and internal capsule, and cortical infarcts in the anterior flow region were associated with an increased risk of depressive symptoms (figure 1). Associations attenuated after adjustment for all covariates (RR=2.02, 95% CI 1.14-3.59; RR=2.25, 95% CI 0.98-5.20), particularly for cortical infarcts (RR=1.89, 95% CI 0.94-3.83). Associations with locations of WML and atrophy were not significant (figure 1).

Table 1 Characteristics of patients 50 years or older with and without depressive symptoms

	Total sample (n=585)	Depressive symptoms (n=102)	No depressive symptoms (n=483)	P-value
Age[¥] (years)	63 ± 7.9	61 ± 7.8	64 ± 7.9	<0.01
Female gender (%)	18	28	16	<0.01
DART score[†]	84 (58-98)	84 (58-96)	84 (58-98)	0.80
Education class[†]	4 (2-7)	4 (1-7)	4 (2-7)	0.74
MMSE score[†]	29 (27-30)	29 (26-30)	29 (27-30)	0.20
Hypertension (%)	63	63	62	0.91
Diabetes mellitus (%)	22	31	20	0.02
Physical functioning[†]	52 (34-57)	43 (28-56)	53 (36-57)	<0.01
Total intracranial volume[¥] (mL)	1457 ± 129	1437 ± 137	1461 ± 127	0.09
Brain parenchymal fraction[¥] (%)	78 ± 2.8	78 ± 2.6	78 ± 2.8	0.20
Ventricular fraction[¥] (%)	2.3 ± 1.0	2.2 ± 1.0	2.3 ± 0.9	0.48
Cortical gray matter fraction[¥] (%)	34 ± 3.4	35 ± 3.4	34 ± 3.3	0.34
Total WML volume[†] (mL)	1.5 (0.4-9.9)	1.4 (0.4-8.3)	1.6 (0.4-10.2)	0.47
Periventricular WML volume[†] (mL)	1.0 (0.2-5.9)	0.8 (0.1-5.7)	1.0 (0.2-6.0)	0.60
Deep WML volume[†] (mL)	0.5 (0.2-3.9)	0.5 (0.1-2.9)	0.5 (0.2-4.3)	0.67
Presence of cerebral infarcts (%)				
- Cortical infarct	14	17	14	0.43
- Subcortical infarct	1	4	1	0.02
- Lacunar infarct	23	22	23	0.80
PHQ-9 score[†]	1 (0-8)	8 (6-13)	1 (0-4)	<0.01
History of depressive episode before age 50 (%)	29	45	26	<0.01

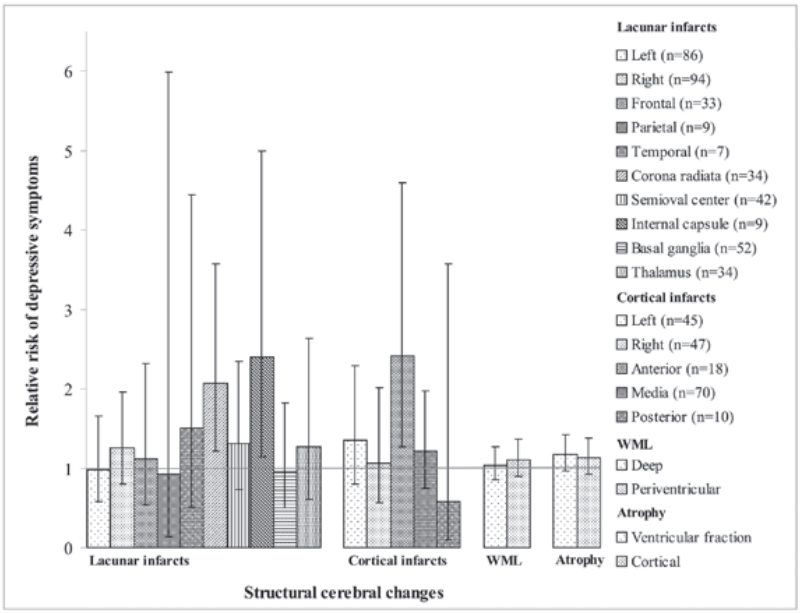
Presence of depressive symptoms is defined as PHQ-9 score ≥6.
DART, Dutch adult reading test; MMSE, Mini-mental state examination; WML, White matter lesion; PHQ-9, Patient health questionnaire-9
[¥] Mean ± SD
[†] Median, (10^{th}-90^{th} percentile)

Table 2 Relative risks (RR) of depressive symptoms associated with indicators of cerebral small-vessel and large-vessel disease and global brain atrophy.

	Depressive symptoms	
	RR	*(95% CI)*
Small-vessel disease		
- Lacunar infarcts (n=133)		
Model I[a]	1.09	(0.71-1.67)
Model II[b]	0.86	(0.56-1.31)
Model III[c]	0.83	(0.53-1.29)
- Total WML[£]		
Model I[a]	1.07	(0.88-1.31)
Model II[b]	1.07	(0.85-1.34)
Model III[c]	1.07	(0.85-1.35)
Large-vessel disease		
- Cortical infarcts (n=82)		
Model I[a]	1.22	(0.78-1.92)
Model II[b]	0.99	(0.63-1.57)
Model III[c]	0.98	(0.57-1.68)
- Large subcortical infarcts (n=7)		
Model I[a]	3.48	(1.76-6.89)
Model II[b]	2.56	(1.29-5.05)
Model III[c]	2.66	(1.28-5.54)
Brain atrophy[£]		
Model I[a]	1.22	(0.97-1.53)
Model II[b]	1.11	(0.85-1.44)
Model III[c]	1.10	(0.85-1.44)

Presence of depressive symptoms is defined as a PHQ-9 score ≥6
WML, White matter lesions; CI, confidence interval; SD, standard deviation
[£] Per SD increase (WML, SD=0.44%; Global brain atrophy, SD=2.77%)
[a] Adjusted for age, sex and education.
[b] Additionally adjusted for hypertension, diabetes mellitus and physical functioning.
[c] Additionally adjusted for co-occurrent infarcts and WML volume

Figure 1 Relative risks of late-life depression, for different locations of lacunar- and cortical infarcts (present versus absent), white matter lesion (WML) volume and global brain atrophy (per SD increase), adjusted for age, sex and education. Error bars indicate 95% confidence intervals.



Excluding patients with first depressive episode before age 50 (n=169), did not change associations with large subcortical infarcts in models I-III (fully adjusted, RR=4.37, 95% CI 2.30-8.29). Lacunar infarcts located in the corona radiata and internal capsule were associated with a similarly increased risk of depressive symptoms in models I-III (fully adjusted, RR=2.04, 95% CI 0.86-4.81; RR=4.49, 95% CI 1.65-12.21), although the first was no longer statistically significant. Associations with cortical infarcts in the anterior flow region were not significant in models I-III (fully adjusted, RR=1.55, 95% CI 0.61-3.94).

Cognitive functioning

Presence of depressive symptoms was significantly associated with poorer memory in models I-II (model II, B=-0.26, 95% CI -0.47 to -0.06), but not with executive functioning (B=-0.09, 95% CI -0.30 to 0.12) or processing speed (B=-0.11, 95% CI -0.30 to 0.08).

Presence of lacunar infarcts and atrophy were significantly associated with worse performance in all domains in models I-II. Associations attenuated after adjustment for infarcts and WML (model III) and were no longer statistically significant, except for processing speed (table 3). Greater WML volume was significantly associated with poorer executive functioning; presence of large subcortical infarcts with poorer executive functioning and memory; and cortical infarcts with slowed processing speed in models I-III (table 3).

Table 3 Analyses with indicators of cerebral small-vessel and large-vessel disease and global brain atrophy as determinants, and z-scores of cognitive domains as outcome variables.

	Executive functioning		**Memory**		**Processing speed**	
	Beta	*(95 % CI)*	*Beta*	*(95 % CI)*	*Beta*	*(95 % CI)*
Small-vessel disease						
- Lacunes (n=133)						
Model I[a]	-0.25	(-0.43 to -0.06)	-0.21	(-0.39 to -0.03)	-0.23	(-0.39 to -0.06)
Model II[b]	-0.24	(-0.42 to -0.05)	-0.19	(-0.38 to -0.01)	-0.22	(-0.38 to -0.05)
Model III[c]	-0.13	(-0.33 to 0.06)	-0.13	(-0.32 to 0.07)	-0.19	(-0.37 to -0.01)
- Total WML[£]						
Model I[a]	-0.13	(-0.21 to -0.05)	-0.08	(-0.16 to -0.00)	-0.04	(-0.12 to 0.03)
Model II[b]	-0.13	(-0.21 to -0.05)	-0.09	(-0.17 to -0.01)	-0.04	(-0.11 to 0.03)
Model III[c]	-0.10	(-0.18 to -0.02)	-0.06	(-0.14 to 0.02)	-0.02	(-0.10 to 0.05)
Large-vessel disease						
- Cortical infarcts (n=82)						
Model I[a]	-0.12	(-0.33 to 0.10)	-0.09	(-0.31 to 0.12)	-0.24	(-0.44 to -0.05)
Model II[b]	-0.12	(-0.34 to 0.10)	-0.08	(-0.30 to 0.13)	-0.24	(-0.44 to -0.05)
Model III[c]	-0.05	(-0.27 to 0.17)	-0.03	(-0.24 to 0.19)	-0.20	(-0.40 to -0.00)
- Subcortical infarcts (n=7)						
Model I[a]	-0.95	(-1.62 to -0.29)	-0.76	(-1.42 to -0.10)	-0.60	(-1.21 to 0.01)
Model II[b]	-0.93	(-1.60 to -0.26)	-0.72	(-1.39 to -0.06)	-0.59	(-1.20 to 0.03)
Model III[c]	-0.88	(-1.55 to -0.21)	-0.68	(-1.35 to -0.02)	-0.47	(-1.08 to 0.14)
Global brain atrophy[£]						
Model I[a]	-0.10	(-0.19 to 0.00)	-0.13	(-0.23 to -0.03)	-0.19	(-0.28 to -0.11)
Model II[b]	-0.10	(-0.20 to 0.00)	-0.12	(-0.22 to -0.02)	-0.20	(-0.29 to -0.11)
Model III[c]	-0.07	(-0.17 to 0.03)	-0.10	(-0.20 to 0.00)	-0.19	(-0.28 to -0.10)

WML, White matter lesions; CI, confidence interval; SD, standard deviation; DART, Dutch Adult Reading Test

[£] Per SD increase (WML, SD=0.44%; Global brain atrophy, SD=2.77%)

[a] Adjusted for age, sex, DART score and education.

[b] Additionally adjusted for hypertension, diabetes mellitus and physical functioning.

[c] Additionally adjusted for co-occurrent infarcts and WML volume

When location was distinguished, lacunar infarcts in the left hemisphere, corona radiata, semioval center and thalamus were significantly associated with poorer executive functioning and memory in model I (figures 2a-b), and lacunar infarcts located in both hemispheres, frontal lobe, corona radiata and semioval center with slowed processing speed (figure 2c). Adjustment for vascular risk factors and physical functioning did not change these results. Associations attenuated in model III; associations of lacunar infarcts located in the semioval

center with poorer executive functioning (B=-0.44, 95% CI -0.73 to -0.15) and processing speed (B=-0.28, 95% CI -0.55 to -0.01), and lacunar infarcts located in the left hemisphere and corona radiata with poorer memory (B=-0.25, 95% CI -0.47 to -0.03; B=-0.35, 95% CI -0.68 to -0.02) remained statistically significant. Greater periventricular WML volume was significantly associated with poorer functioning in all domains and deep WML volume with executive functioning in model I. Only the association of periventricular WML with executive functioning remained significant in model III (B=-0.17, 95% CI -0.25 to -0.09). Cortical infarcts in the anterior flow region were associated with poorer executive functioning, cortical infarcts in the left hemisphere and media flow region and cortical atrophy with slowed processing speed, and greater ventricular volume with poorer performance in all cognitive domains in model I (figures 2a-c). Only associations of left sided and media cortical infarcts, ventricular volume and cortical atrophy with slowed processing speed remained significant after adjustment for other infarcts and WML (data not shown).

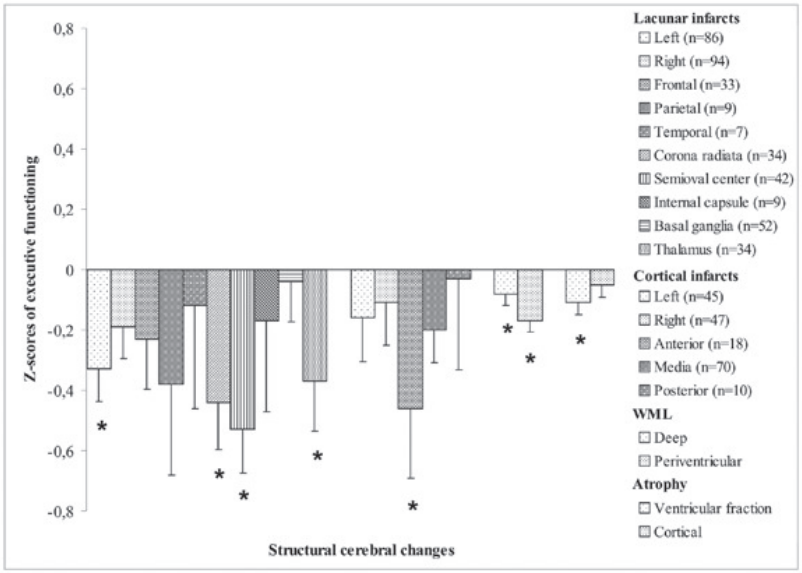


Figure 2a Z-scores of executive functioning for different locations of lacunar and cortical infarcts (present versus absent), white matter lesion (WML) volume and global brain atrophy (per SD increase), adjusted for age, sex, DART score and education. Error bars indicate standard errors. Statistically significant associations are illustrated with an asterix.

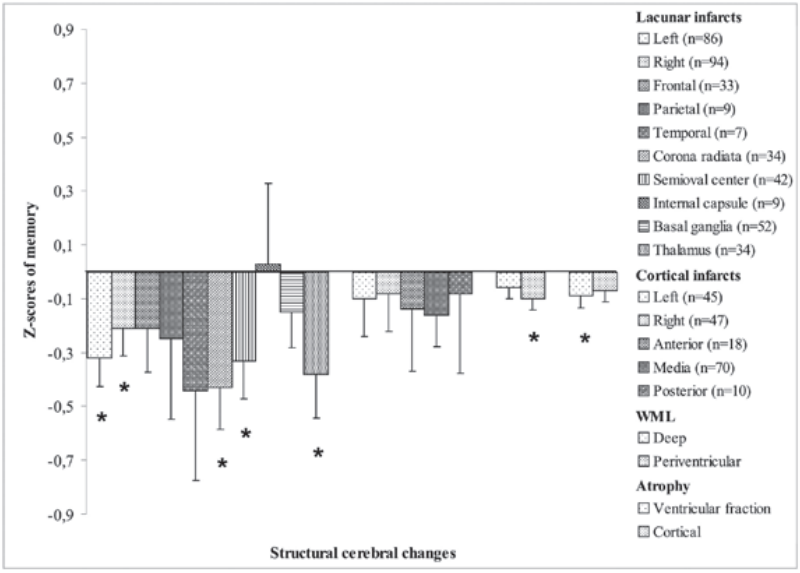


Figure 2b Z-scores of memory for different locations of lacunar and cortical infarcts (present versus absent), white matter lesion (WML) volume and global brain atrophy (per SD increase), adjusted for age, sex, DART score and education. Error bars indicate standard errors. Statistically significant associations are illustrated with an asterix.

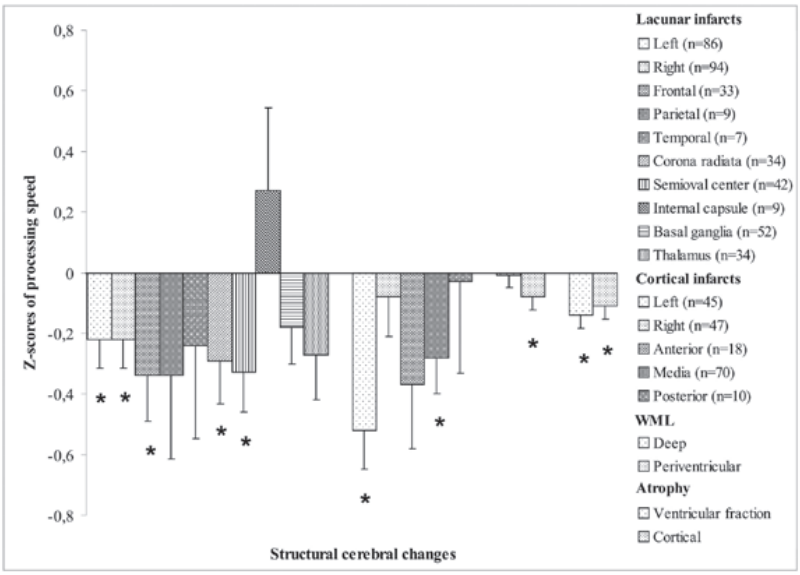


Figure 2c Z-scores of processing speed for different locations of lacunar and cortical infarcts (present versus absent), white matter lesion (WML) volume and global brain atrophy (per SD increase), adjusted for age, sex, DART score and education. Error bars indicate standard errors. Statistically significant associations are illustrated with an asterix.

Discussion

In a cohort of non-demented elderly with symptomatic atherosclerotic disease, we observed that memory functions were significantly lower in patients with depressive symptoms. As hypothesized, small and large-vessel subcortical infarcts located in projecting deep white matter tracts were associated with an increased risk of depressive symptoms as well as poorer executive functioning and memory. Periventricular WML volume was associated with poorer executive functioning, but not with depressive symptoms. The finding that cortical infarcts in the left hemisphere and media flow region and atrophy were associated with slowed processing speed was in line with our second hypothesis.

Main strengths of our study include the extensive information on different types and locations of brain changes on MRI, and the elaborate cognitive test battery, assessing different domains of cognitive functioning. In addition, volumetric MRI measurements enabled more accurate WML and atrophy estimations, and are less influenced by observer-bias than visual rating methods [41]. Also, associations were adjusted for various potentially important confounders.

Previously, a large community-based study found that lacunar infarcts in the basal ganglia and severe WML were associated with an increased risk of depressive symptoms in later life [17]. Another study reported somewhat contradictory findings, suggesting that deep WML but not lacunar infarcts were associated with depressive symptoms [18,20]. Others could not demonstrate any effect of WML severity or location on depressive symptoms [8,22]. Differences in findings between our study and other studies may be explained by differences in the classification of the location of lacunar infarcts. In addition, previous studies often relied upon visual assessment of brain lesions, complicating the comparison of estimates obtained with volumetric methods. Furthermore, most cohort studies included population-based samples, whereas our study sample consisted of patients with symptomatic atherosclerotic disease. The influence of small-vessel changes on depressive symptoms might be attenuated in patients at high vascular risk or with existing atherosclerotic disease. This hypothesis is supported by our finding that adjustment for vascular risk factors attenuated associations of MRI variables with depressive symptoms.

Previously, the strategic location of lacunar infarcts in the basal ganglia and thalamus has been associated with poorer executive functioning and memory in the LADIS study [16]. Further, a study in non-disabled elderly reported that greater periventricular WML severity was associated with slowed processing speed [19]. In contrast, a study in subjects with mild cognitive impairment suggested that only deep WML were associated with poorer executive functioning and processing speed [21]. Our data suggest that lesion types are differentially associated with poorer performance in specific cognitive domains, and that these associations

strongly depend on lesion location. As hypothesized, subcortical infarcts in projecting white matter tracts were most strongly associated with poorer executive functioning and memory, whereas WML volume was associated with poorer executive functioning only. Cortical infarcts affecting the frontal lobe were also associated with poorer executive functioning, although not statistically significant. Consistent with our hypothesis, cortical infarcts in the parietotemporal flow region were associated with slowed processing speed. Differences in patient characteristics and overall cognitive performance between our study and previous studies could have contributed to different findings. Few subjects (1.4%) in our sample scored below the normal range of global cognitive function (MMSE <24) [34]. Also, crude scores for immediate and delayed recall, mental flexibility, attention, processing speed and intelligence of our study population were comparable to age- and education adjusted scores in another study that included independently living men of similar age [42]. In this respect, our population had, on average, normal age-adjusted cognitive performance. Further, the majority of studies did not adjust their analyses for co-occurrent infarcts or WML. Our data illustrate that some of the findings were explained by other infarcts or WML, emphasizing the importance of statistical adjustment for other structural changes. Finally, associations of infarcts with cognitive function could be mediated by time since lesion onset [14].

A limitation of this study is the cross-sectional design, and we therefore do not know whether brain changes directly contributed to depressive symptoms and poorer cognitive functioning. Further, to assess depressive symptoms, a cut-off value ≥6 on the Patient Health Questionnaire-9 was used and although this cut-off has been recommended for patients with vascular risk [27] it could have created a relatively wide range of severity of depressive symptoms in patients classified as having depressive symptoms, resulting in a decreased contrast between patients with and without depressive symptoms. Also, the largest effect of ischemic infarcts on depressed mood and cognitive function would be expected in patients suffering most severe strokes. Because these patients are less likely to participate in our study, this could have contributed to a relative underestimation of the effects. In addition, despite the large sample size, the number of infarcts in distinct anatomic locations was limited, contributing to relatively wide confidence intervals and possibly to non-significant associations.

In summary, we found that subcortical infarcts contributed to an increased risk of depressive symptoms as well as poorer executive functioning and memory. This depended on location in deep white matter tracts and not on infarct size. Cortical infarcts in parietotemporal regions, WML and atrophy were associated with worse cognitive functioning, but not with depressive symptoms. Longitudinal studies are needed to assess whether cerebral changes directly contribute to the development of depressive symptoms and impaired cognitive functioning.

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Chapter 4.2

Response to 'Localization of white-matter lesions and effect of vascular risk factors in late-onset major depression'

Anne M. Grool, Koen L. Vincken, Yolanda van der Graaf and Mirjam I. Geerlings

Psychol Med 2010; 40:1229-1230

Letter to the Editor

Recently, Dalby et al published an interesting paper on the associations of localization, number and volume of deep white matter lesions (DWML) with late-onset depression, using a case-control design in which they compared 22 patients with late-onset major depression to 22 healthy controls [1]. The authors found a relation between DWML localization and late-onset depression, whereas no associations of DWML number and volume with late-onset depression were found. We read this paper with great interest, and although their findings could be of importance, we have a number of considerations when interpreting the findings.

First, DWML were identified on axial FLAIR images (matrix 224x256, slice thickness 5 mm) and manually labelled by one trained neuroradiologist. When axially viewed, deep lesions may appear to be present on MRI. However, when sagital and coronal orientations are viewed, many of these lesions are actually contiguous with the ventricular lining and may therefore be incorrectly classified as 'deep' [2]. Also, volume estimations from manually labelled WML have a lower reproducibility and objectivity than estimations from automated segmentation programmes, and often lead to a relative volume overestimation. When WML are visually labelled, all hyperintensities are given the same probability to be lesion volumes, since no distinctions are made in hyperintensity range. In addition, less hyperintense voxels around and within lesions are also counted as WML volume, which is likely to result in greater WML volumes than probabilistically estimated volumes. The aforementioned situations could result in a relative overestimation of deep WML volume, which is in agreement with the high number of individuals displaying deep WML in Dalby et al's study sample (17 of 22 patients, and 21 of 22 controls). The authors did not report the median volume of DWML in patients and controls, but when we calculated this from figure 1, it was approximately 0.4 mL for patients and 0.5 mL for controls. These volumes are quite high, given the relatively young age and low prevalence of vascular risk factors in this population. Recently, we reported that volumetrically assessed median DWML volume was 0.4 mL in a large sample of patients with symptomatic atherosclerotic disease (mean age 58 ± 10 years), while they had more vascular risk factors than Dalby et al's study sample [3]. Another study, in patients with evidence of vascular disease or at high risk of developing vascular disease of considerably older age (mean age 75 ± 3 years), found a median DWML volume of 0.5 mL [4].

Secondly, because of the relatively small sample size, patients with extremely high or low values of DWML volume seem to distort the findings. In figure 1, three patients with extremely high values are seen in the control group. When these patients are left out, the median volume seems to decrease to 0.18 mL. Also, in the patient group three outliers are seen with low values. Exclusion of these outliers seems to increase median DWML volume

to 0.53 mL. A significant difference in WML volume between depressed and control subjects could have been present if these outliers were excluded from the analyses. Hence, it would have been preferable to use a larger sample size.

Third, when control subjects are recruited through advertisement, it is important to take the possibility of selection bias into consideration. Since not all people have access to the source of the advertisement, some members of the population are less likely to be included than others, leading to a biased and unrepresentative sample. Self-selection can also play an important role in recruitment through advertisement. A participants' decision to participate may be correlated with traits that affect the study, creating a non-representative control sample, thereby inducing incomparability between patients and controls.

Finally, the last hypothesis tested by the authors was that vascular risk factors have a significant effect on WML load. Most previous studies found that vascular risk factors, including hypertension and diabetes mellitus, are significantly associated with WML load. Dalby et al did not find a significant effect of these variables on WML load. This may be a result of matching the depressed patients with control subjects for age, gender and vascular risk factors. A consequence of matching is that these factors can no longer be studied as a determinant of the outcome, because all variation is 'matched away'. A significant difference was however found in social class between depressed and control subjects. Unfortunately, the authors did not adjust for the difference in socioeconomic class, whereas such an adjustment might have influenced the results.

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Chapter 5

Location of cerebral small-vessel disease and depressive symptom profiles

Chapter 5.1

Location and progression of cerebral small-vessel disease and atrophy, and depressive symptom profiles. The SMART-Medea study

Anne M. Grool, Yolanda van der Graaf, Willem P.T.M. Mali, Theo D. Witkamp, Koen L. Vincken and Mirjam I. Geerlings on behalf of the SMART Study Group.

Psychol Med 2012; 42:359-370

Abstract

Objectives

The 'vascular depression' hypothesis states that brain changes located in frontal-subcortical pathways increase vulnerability of specific depressive symptom profiles, but studies examining locations of small-vessel and degenerative changes with individual symptoms are scarce. We examined whether location and progression of white matter lesions (WML), lacunar infarcts and atrophy were associated with motivational and mood symptoms in patients with symptomatic atherosclerotic disease.

Methods

In 578 patients (63±8 years) of the SMART-Medea study, volumes of WML and atrophy and visually rated infarcts were obtained with 1.5T MRI at baseline and after 3.9±0.4 years follow-up. Depressive symptoms were assessed with Patient Health Questionnaire-9 at follow-up and categorized into motivational and mood symptoms.

Results

Regression analyses adjusted for age, sex, education, MMSE, physical functioning, antidepressant use and vascular risk factors, showed that location in mainly deep white matter tracts and progression of WML were associated with symptoms of anhedonia, concentration problems, psychomotor retardation and appetite disturbance. Lacunar infarcts in deep white matter were associated with greater motivational (RR=1.7, 95%CI 1.2-2.4) and mood (RR=1.7, 95%CI 1.1-2.6) sumscores, and with symptoms of psychomotor retardation, energy loss and depressed mood; lacunar infarcts in the thalamus were associated with psychomotor retardation only. Cortical atrophy was associated with symptoms of anhedonia and appetite disturbance. Excluding patients with major depression did not materially change the results.

Conclusions

Our findings suggest that disruption of frontal-subcortical pathways by small-vessel lesions leads to a symptom profile that is mainly characteristic of motivational problems, also in the absence of major depression.

Introduction

Atrophy and cerebral small-vessel changes, characterized by white matter lesions (WML) and lacunar infarcts, are common findings on magnetic resonance imaging (MRI) in the elderly [1,2], and result from loss of the neuronal and dendritic architecture and chronic or acute ischemia, leading to incomplete infarction, demyelination and concomitant necrosis [3,4]. Although atrophy and small-vessel changes are often asymptomatic, they have been associated with an increased risk of cognitive impairment [5] and late-life depression [6,7].

The underlying mechanisms contributing to the increased risk of late-life depression are not yet fully understood. The 'vascular depression' hypothesis postulates that small-vessel lesions predispose to late-life depression by disrupting emotion-regulating prefrontal structures or their modulating pathways [8,9]. In addition, age-related degenerative changes could also play a role in the disruption of emotion-regulating pathways [10]. Motivational symptoms are considered as a dominant feature of vascular depression, including psychomotor retardation and loss of interest [11,12].

Direct evidence supporting the hypothesis that disruption of frontal-subcortical pathways by small-vessel or degenerative changes is associated with a motivational symptom profile is scarce, because few studies have examined whether specific locations of small-vessel and degenerative changes were associated with characteristic depressive symptoms. Studies that have examined the anatomic location of cerebral changes on MRI often did not assess individual depressive symptoms, but an overall depressive symptom score [6,13]. One study that did, observed that deep WML severity was associated with symptoms of impaired motivation, concentration and decision making, but associations with lacunar infarcts and atrophy were not assessed [14]. Others reported that subcortical small-vessel lesion severity was associated with an increased risk of apathy in subjects with major depression, but lesion location was not distinguished [15]. In addition, a direct relation between cerebral changes on MRI and depressive symptoms is more likely if greater lesion progression increases the risk of motivational or mood symptom profiles, but no studies have examined this.

We examined whether the location and progression of WML, lacunar infarcts and atrophy were associated with an increased risk of mood or motivational symptom profiles in patients with symptomatic atherosclerotic disease. In addition, we excluded patients with major depressive disorder to investigate whether associations were independent of depressive state. We expect that as a result of their vascular burden, these patients are more vulnerable for the presence of cerebrovascular and degenerative changes than the general population.

Materials and methods

Subjects

Data were used from the Second Manifestations of ARTerial disease—Magnetic Resonance (SMART-MR) study, a prospective cohort study intended to investigate brain changes on magnetic resonance imaging (MRI) in 1309 independently living patients with symptomatic atherosclerotic disease. Details of the design and participants have been described elsewhere [16]. In brief, between May 2001 and December 2005, all patients newly referred to the University Medical Center Utrecht with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, or an abdominal aortic aneurysm (AAA), and without MR contraindications, were invited to participate. During a 1-day visit to our medical center, an MRI of the brain, physical examination, blood and urine sampling were performed. Risk factors, medical history, and functioning were assessed with questionnaires.

Between January 2006 and May 2009, all participants still alive were invited for follow-up measurements, including MRI of the brain, neuropsychological testing, a physical examination, blood and urine sampling, risk factors, medical history, and functioning. In addition, as part of the SMART-Medea (Memory, depression and aging) study, an ancillary study to the SMART-MR study, intended to investigate brain changes associated with psychosocial vulnerability and stress factors, measurements of depression were added from March 2006. The SMART-MR and SMART-Medea study were approved by the ethics committee of our institution, and after complete description of the study to the subjects, written informed consent was obtained from all participants. In total, 754 of the surviving cohort (61% of n=1238) gave written informed consent; 466 (38%) persons refused, and 18 (1%) were lost to follow-up.

Magnetic Resonance Imaging Protocol

MR investigations were performed at baseline and follow-up on a 1.5-Tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE): 235/2 ms; flip angle, 80º), a transversal T2-weighted turbo spin-echo sequence (TR/TE: 2200/11 ms and 2200/100 ms; turbo factor 12), a transversal T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI): 6000/100/2000 ms) and a transversal inversion recovery (IR) sequence (TR/TE/TI: 2900/22/410 ms) (field of view 230x230 mm; matrix size, 180x256; slice thickness, 4.0 mm; no slice gap; 38 slices).

Brain segmentation

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique has been described elsewhere [17,18].

The segmentation program distinguishes cortical gray matter, white matter, sulcal and ventricular cerebrospinal fluid (CSF), and lesions. The results of the segmentation analysis were visually checked for the presence of infarcts and adapted if necessary to make a distinction between WML and infarct volumes. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, the volumes of WML and infarcts. All volumes cranial to the foramen magnum were included. As a result, the total brain volume includes the cerebrum, brainstem and cerebellum. Total intracranial volume (ICV) was calculated by summing the total brain volume and the volumes of the sulcal and ventricular CSF. At baseline, the IR and T1-weighted sequence were missing in 188 patients due to a temporary change in MRI protocol, and the brain segmentation was based on the FLAIR sequence. Intraclass correlation coefficients between the segmentation using all 3 sequences and FLAIR only based on a subset of 740 patients were 0.995, 0.996, 0.961, 0.996, and 0.985 for ICV, total brain volume, CSF, ventricular volume, and white matter lesion volume, respectively.

Infarcts and white matter lesions

The whole brain was visually searched for infarcts by a trained investigator and a neuroradiologist. Raters were blinded to the history and diagnosis of the patient. Discrepancies in rating were re-evaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images in order to distinguish them from WML. Peri-lesional hyperintensity surrounding a lacunar infarct was considered as infarct volume and not as white matter lesion volume. Dilated perivascular spaces were distinguished from infarcts on the basis of their location (along perforating or medullary arteries, often symmetric bilaterally, usually in the lower third of the basal ganglia or centrum semiovale), form (round/oval), and the absence of gliosis. The location, affected flow territory and type were scored for every infarct. Brain infarcts were categorized as cortical infarcts, lacunar infarcts, large subcortical infarcts and infratentorial infarcts. Large subcortical infarcts were sized >15 mm and were not confluent with cortical infarcts. We defined lacunar infarcts as infarcts of 3 to 15 mm in diameter and located in the frontal, parietal, temporal and occipital lobes, corona radiata, internal capsule, semioval center, thalamus or basal ganglia. Infratentorial infarcts were located in the brainstem or cerebellum. Periventricular lesions were defined as WML adjacent to or within 1 cm of the lateral ventricles in both hemispheres. Deep lesions were located in the deep white matter tracts and may or may not have adjoined periventricular lesions. Volumes of periventricular and deep WML were summed to obtain the total volume of WML. Volumes of WML were normalized for regular subject variations by expressing WML volumes as percentage of ICV.

Brain volumes

All brain volumes (total brain volume, ventricular volume and cortical gray matter volume) were expressed relative to ICV. Brain parenchymal fraction (BPF) was used as an indicator of global brain atrophy, ventricular volume as an indicator of subcortical brain atrophy, and cortical gray matter volume as an indicator of cortical brain atrophy.

Depressive symptom profiles

At the follow-up exam of SMART-MR, as part of SMART-Medea, depressive symptoms were measured with the Patient Health Questionnaire-9 (PHQ-9) [19,20]. It assesses the presence of the nine DSM-IV symptoms for major depressive disorder in the past two weeks. Responses are scored on a 4-point Likert scale of 0 to 3, indicating that the participant experienced the symptom "not at all", "on several days", "on more than half the days" or "nearly every day", with higher scores indicating more severe symptoms. According to previously reported classifications, we distinguished motivational (anhedonia, energy loss, concentration problems and psychomotor retardation) and mood profiles (depressed mood, appetite disturbance, feelings of guilt and suicidal thoughts) by counting the positively rated criteria (score range 0-12) [21,22]. Sleep disturbance was not included in either profile [21,22]. In addition, we dichotomized the nine individual items into presence ("several days" to "nearly every day") or absence ("not at all") of symptoms in line with recently recommended cut-off scores [23].

The presence of major depressive disorder (MDD) in the preceding 12 months was assessed in all participants according to DSM-IV criteria [24] using the Composite International Depression Interview (CIDI, version 2.1) [25].

Other variables

Educational level was divided into eight categories, graded from primary school to academic degree, according to the Dutch educational system. During the visit to the medical center, an overnight fasting venous blood sample was taken to determine lipid and glucose levels. Height and weight were measured without shoes and heavy clothing, and body mass index (BMI) was calculated (kg/m^2). Systolic and diastolic blood pressures (mm Hg) were measured three times with a sphygmomanometer and averaged. Hypertension was defined as mean systolic blood pressure ≥160 mm Hg, mean diastolic blood pressure ≥95 mm Hg or self reported antihypertensive drug use. Hyperlipidemia was defined as total cholesterol >5.0 mmol/L, low-density lipoprotein cholesterol >3.2 mmol/L or self reported use of lipid lowering drugs. Diabetes mellitus was defined as a history of diabetes mellitus, glucose ≥7.0 mmol/L or self reported use of oral antidiabetic drugs or insulin. Type and dose of antidepressant medication, smoking habits and alcohol intake were assessed with questionnaires. Pack-

years of smoking was calculated, and alcohol use was categorized into <1 drink p/week, 1-20 drinks p/week, and >20 drinks p/week. Physical functioning was assessed with the Physical Component Summary scale of the Short Form-12 (SF-12), a shortened version of the Short Form-36 (SF-36) Medical Outcomes Study Health Survey [26].

Global cognitive functioning was measured with the Mini-Mental State Examination (MMSE) [27]. Executive functioning was assessed with three tests. The visual elevator test (subtest of the Test of Everyday Attention [28]) is a timed test of 10 trials that measures mental flexibility and shifting of attention. The Brixton Spatial Anticipation test [29] was used to assess the capacity to discover logical rules and mental inhibition and flexibility. The Verbal Fluency test was used to assess mental flexibility and employment of strategies. Before calculating z-scores, scores of the Visual Elevator test and Brixton Spatial Anticipation test were multiplied by minus one, so that lower scores represented poorer performance. A composite z-score was computed by averaging z-scores of the three subtests.

Study sample

Of the 754 patients participating at follow-up, all patients aged 50 years or older (n=680) were included in the current study. Of these, data on MRI variables was missing in 56 patients (no MRI: 40, motion or artefacts: 16). Of the remaining 624 patients, the PHQ-9 questionnaire was missing in 11 patients, and data on covariates in 35 patients. This resulted in a cross-sectional analytical sample of 578 patients (figure 1). For analyses on lesion progression we used data of 553 patients, because data on baseline MRI variables was missing in 25 patients (no MRI: 4, motion or artefacts: 21).

No significant differences in patient characteristics were found between patients with missing data and our cross-sectional sample, except for lower MMSE score (median, 28.5 (26-30) versus 29.0 (27-30), p=0.01).

Data analysis

Because of overdispersion of the positively skewed component scores, we used negative binomial regression analysis to investigate the cross-sectional relationships between location of WML volume, lacunar infarcts and atrophy as independent variables, and motivational and mood component scores as dependent variables. Using negative binomial regression analysis, incidence rate ratios can be calculated. In addition, we investigated relationships between location of WML volume, lacunar infarcts and atrophy with individual depressive symptoms using log binomial models and Poisson regression models with robust standard errors. We estimated relative risks and accompanying confidence intervals (CI) [30,31] rather than odds ratios, which overestimate the relative risk, particularly for outcomes that are

common (>10%) [32,33]. WML volume (% of ICV) and atrophy were first entered in quartiles, with the lowest quartile serving as reference category to check for non-linear relations, and then entered on a continuous scale (per SD increase) if the association was linear to increase precision. Locations of lacunar infarcts were divided into frontal, deep white matter (corona radiata, semioval center or internal capsule), other white matter (parietal, temporal or occipital lobe), thalamus and basal ganglia. In model I, associations were adjusted for age, sex, education and MMSE score. We additionally adjusted for physical functioning, antidepressant use, smoking, alcohol use, BMI, hyperlipidemia, hypertension and diabetes mellitus in a separate model (model II), because it is not clear to what extent these vascular risk factors are confounders or preceding factors in the pathway between small-vessel lesions or atrophy and depressive symptoms, or both.

Next, we investigated the relationship between progression of cerebral changes during 3.9±0.4 years of follow-up and depressive symptoms at follow-up. Progression of WML volume and atrophy was defined as difference in WML volume (% of ICV) and brain parenchymal fraction between baseline and follow-up, and was dichotomized into the highest quartile versus the three lowest quartiles. Progression of lacunar infarcts was defined as any new lacunar infarct between baseline and follow-up. All three progression measures were entered in the same model; adjustment for covariates was performed as described above.

As final step, all the above described analyses were additionally adjusted for the diagnosis of atherosclerotic disease at inclusion (model III).

In additional analyses, we examined associations of executive functioning with motivational and mood profile scores and individual symptoms. To investigate whether poorer executive functioning could be a confounder or intermediate factor in the pathway between cerebral changes and depressive symptoms, we additionally adjusted model II for z-score of executive functioning.

To investigate whether associations of degenerative and small-vessel changes in fronto-subcortical regions with symptom profiles were independent of depressive status, we repeated the analyses of location and progression of cerebral changes with profile scores and individual symptoms, after excluding patients with major depressive disorder (n=35).

Finally, we repeated the analyses of location and progression of cerebral changes with profile scores and individual symptoms after exclusion of patients with a cortical infarct (n=84) or large subcortical infarct (n=3), to examine whether associations were influenced by the presence of these infarcts.

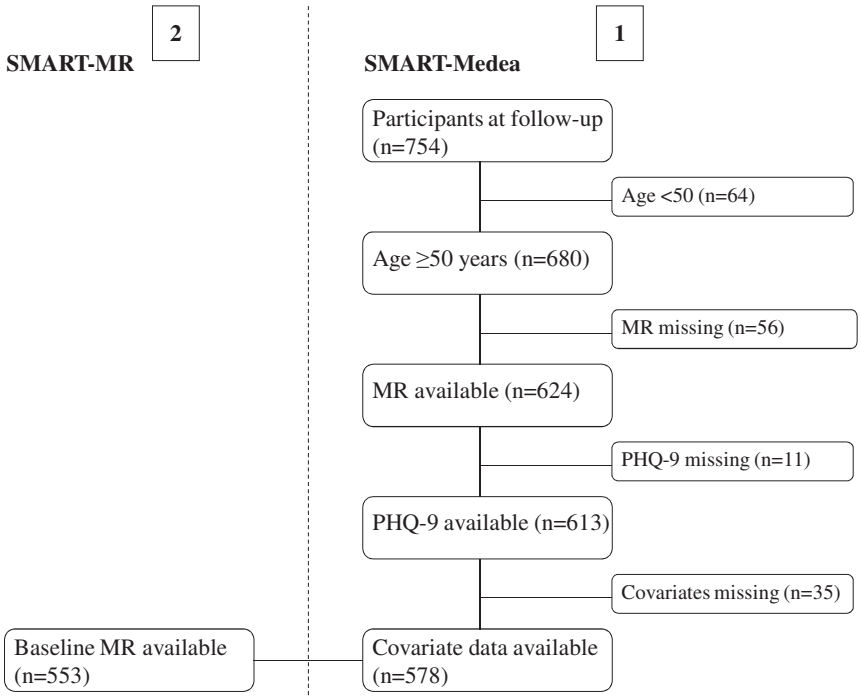

Figure 1 Flowchart illustrating the composition of the study sample for cross-sectional analyses on SMART-Medea data [1] and for longitudinal analyses including baseline data on MRI variables [2].

Results

Of the study sample, 136 patients (24%) were included at baseline with cerebrovascular disease; 362 (63%) were included with coronary artery disease; 104 (18%) were included with peripheral arterial disease; and 40 (7%) were included with abdominal aortic aneurysm. Patient characteristics at follow-up are summarized in table 1. Mean age was 63±8 years and 17% of the sample was female. Median PHQ-9 score was low, but most individual symptoms were frequently reported.

Location of cerebral changes

White matter lesion volume

Increased periventricular and deep WML volumes were not significantly associated with greater motivational and mood profile scores after adjustment for age, sex, education and MMSE (table 2). When individual symptoms were distinguished, larger periventricular WML volume was associated with an increased risk of anhedonia (RR=1.19, 95% CI 1.04-1.35) and appetite disturbance (RR=1.19, 95% CI 1.01-1.40), and larger deep WML volume with anhedonia (RR=1.18, 95% CI 1.09-1.27), energy loss (RR=1.08, 95% CI 1.02-1.15), appetite disturbance (RR=1.20, 95% CI 1.09-1.32) and concentration problems (RR=1.15, 95% CI 1.05-1.26) in model II.

Table 1 Patient characteristics (n=578)

	All subjects (n=578)
Age[¥] (years)	63 ± 7.9
Female gender	17
Smoking[†] (pack-years)	20 (0-51)
Alcohol use (%)	
- <1 drink p/week	29
- 1-20 drinks p/week	60
- >20 drinks p/week	11
BMI[¥] (kg/m^2)	27 ± 3.8
Hyperlipidemia (%)	83
Hypertension (%)	63
Diabetes mellitus (%)	23
Total intracranial volume[¥] (mL)	1459 ± 129
Absolute total WML volume[†] (mL)	1.5 (0.4-9.6)
- Periventricular WML volume[†] (mL)	1.0 (0.2-5.9)
- Deep WML volume[†] (mL)	0.5 (0.2-3.8)
Lacunar infarcts (%)	23
Brain parenchymal fraction[¥] (%)	78 ± 2.8
- Ventricular fraction[¥] (%)	2.3 ± 1.0
- Gray matter fraction[¥] (%)	34 ± 3.5
MMSE score[†]	29 (27-30)
Physical functioning[†]	52 (34-57)
PHQ-9 score[†]	1 (0-8)
- Motivational profile score[†]	1 (0-4)
- Mood profile score[†]	1 (0-2)
Individual symptoms (%)	
- Anhedonia	26
- Depressed mood	19
- Sleep disturbance	42
- Loss of energy	49
- Change of appetite	17
- Feelings of guilt	12
- Concentration problems	26
- Psychomotor retardation	9
- Suicidal thoughts	4
Antidepressant use (%)	7

WML, White Matter Lesion; MMSE, Mini-Mental State Examination; PHQ-9, Patient Health Questionnaire-9

[£] Presence of individual symptoms was defined as a score of "several days" to "nearly every day"

[¥] Mean ± SD

[†] Median, (10th-90th percentile)

Lacunar infarcts

Patients with lacunar infarcts in the deep white matter (figure 2) compared to those without, while holding all other variables constant in the model, had a rate 1.7 times greater for mood profile score, and a rate 1.7 times greater for motivational profile score, while lacunar infarcts in other locations were not associated with increased rates (table 2). When we distinguished individual depressive symptoms, presence of lacunar infarcts in the deep white matter increased the risk of energy loss (RR=1.34, 95% CI 1.07-1.68), psychomotor retardation (RR=2.68, 95% CI 1.48-4.86) and depressed mood (RR=1.69, 95% CI 1.08-2.64) in model II. In addition, lacunar infarcts in the thalamus were associated with psychomotor retardation (RR=2.67, 95% CI 1.25-5.74, model II).

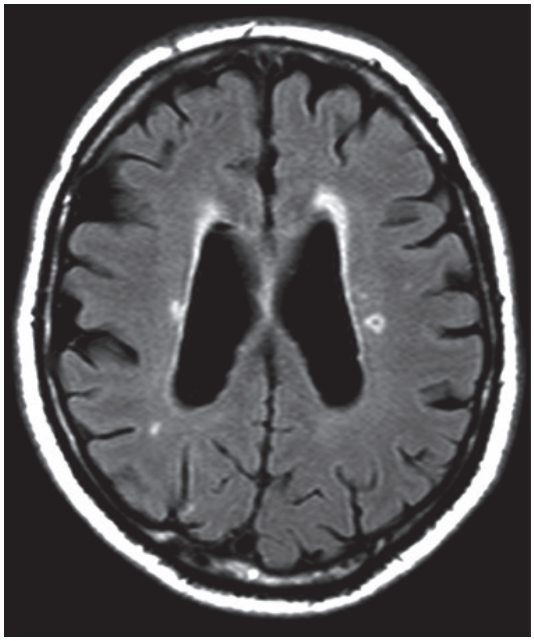

Figure 2 T2-weighted fluid attenuating inverse recovery (FLAIR) image illustrating a lacunar infarct in the corona radiata in the left hemisphere.

Atrophy

Associations of greater subcortical or cortical atrophy with motivational and mood profile scores were not significant (table 2). When individual symptoms were distinguished, subcortical atrophy increased the risk of energy loss (RR=1.12, 95% CI 1.03-1.22) and feelings of guilt (RR=1.26, 95% CI 1.03-1.55) in model I; associations attenuated and became non significant in model II (data not shown). Cortical atrophy was significantly associated with anhedonia (RR=1.20, 95% CI 1.03-1.39) and appetite disturbance (RR=1.24, 95% CI 1.01-1.51) in model II.

Table 2 Results of regression analyses with locations of white matter lesion volume, lacunar infarcts and atrophy as independent, and depressive symptom profiles as dependent variables (n=578)

	Motivational profile score		Mood profile score	
	IRR	**(95% CI)**	**IRR**	**(95% CI)**
White matter lesion volume¥				
- Deep				
Model I[a]	1.08	(0.98-1.19)	1.08	(0.96-1.22)
Model II[b]	1.11	(1.00-1.23)	1.05	(0.92-1.19)
- Periventricular				
Model I[a]	1.09	(0.97-1.22)	1.13	(0.99-1.30)
Model II[b]	1.09	(0.97-1.23)	1.07	(0.93-1.24)
Lacunar infarcts				
- Frontal lobe				
Model I[a]	1.01	(0.62-1.65)	0.78	(0.40-1.51)
Model II[b]	0.77	(0.45-1.31)	0.54	(0.26-1.13)
- Deep white matter				
Model I[a]	1.71	(1.23-2.36)	1.89	(1.27-2.81)
Model II[b]	1.72	(1.21-2.44)	1.72	(1.12-2.63)
- Other white matter				
Model I[a]	1.24	(0.70-2.20)	1.67	(0.87-3.24)
Model II[b]	1.02	(0.56-1.86)	1.34	(0.67-2.69)
- Thalamus				
Model I[a]	1.55	(0.99-2.43)	1.24	(0.70-2.20)
Model II[b]	1.10	(0.66-1.81)	0.97	(0.51-1.82)
- Basal ganglia				
Model I[a]	1.23	(0.84-1.79)	1.41	(0.89-2.22)
Model II[b]	1.07	(0.71-1.61)	1.24	(0.75-2.05)
Atrophy¥				
- Subcortical				
Model I[a]	1.13	(1.00-1.27)	1.14	(0.98-1.32)
Model II[b]	1.10	(0.96-1.25)	1.06	(0.90-1.24)
- Cortical				
Model I[a]	1.13	(1.01-1.28)	1.16	(1.00-1.33)
Model II[b]	1.09	(0.96-1.24)	1.10	(0.94-1.28)

IRR, Incidence rate ratio; CI, Confidence interval; MMSE, Mini-mental state examination

¥ Per SD increase (white matter lesions: deep, 0.27%, periventricular, 0.23%; atrophy: subcortical, 0.96%, cortical, 3.48%)

[a] Adjusted for age, sex, education and MMSE

[b] Additionally adjusted for physical functioning, antidepressant use, smoking, alcohol intake, body mass index, hyperlipidemia, hypertension and diabetes mellitus

Progression of cerebral changes

Patients in the highest quartile of progression of WML volume (>0.08% of ICV increase in WML volume) had significantly greater motivational profiles scores than patients in the three lowest quartiles of WML progression in model I (table 3), independent of progression of lacunar infarcts or atrophy. The association attenuated and became non significant in model II. When individual depressive symptoms were distinguished, greater progression of WML volume increased the risk of anhedonia (RR=1.44, 95% CI 1.05-1.98), appetite disturbance (RR=1.55, 95% CI 1.00-1.40), concentration problems (RR=1.68, 95% CI 1.24-2.29) and psychomotor retardation (RR=2.43, 95% CI 1.35-4.35) in model II.

Progression of lacunar infarcts between baseline and follow-up (8% of patients) was not significantly associated with greater motivational and mood profile scores (table 3), or with individual symptoms (data not shown).

Patients in the highest quartile of progression of atrophy (>1.70% decrease in brain parenchymal fraction) had significantly greater mood profiles scores than patients in the three lowest quartiles of atrophy progression in model I (table 3). The association attenuated and became non significant in model II. Associations of progression of atrophy with individual symptoms were not statistically significant (data not shown).

Diagnosis of atherosclerotic disease at inclusion

Additional adjustment for diagnosis of atherosclerotic disease at inclusion resulted in similar effect estimates and significance levels, except associations of lacunar infarcts in deep white matter (RR=1.86, 95% CI 0.98-3.53) and thalamus (RR=1.89, 95% CI 0.86-4.16) with psychomotor retardation attenuated and were no longer statistically significant.

Executive functioning

One SD decrease in z-score of executive functioning was not significantly associated with greater motivational or mood profile scores in model II (data not shown). When individual symptoms were distinguished, one SD decrease in z-score of executive functioning was associated with a 1.28 (95% CI 1.01-1.62) times increased risk of psychomotor retardation only in model II.

Entering executive functioning to the model with cerebral changes and depressive symptoms did not change the estimates or significance levels, except for a modest attenuation of the association of lacunar infarcts in deep white matter and thalamus with psychomotor retardation (RR=2.53, 95% CI 1.41-4.52; RR=2.51, 95% CI 1.17-5.37).

Table 3 Results of regression analyses with progression of white matter lesion volume, lacunar infarcts and atrophy as independent, and depressive symptom profiles as dependent variables (n=553)

	Motivational profile score		Mood profile score	
	IRR	**(95% CI)**	**IRR**	**(95% CI)**
White matter lesion volume†				
Model I[a]	1.35	(1.04-1.96)	1.37	(0.98-1.90)
Model II[b]	1.29	(0.97-1.71)	1.28	(0.89-1.84)
Lacunar infarcts				
Model I[a]	1.12	(0.76-1.66)	1.03	(0.63-1.71)
Model II[b]	0.94	(0.61-1.45)	1.07	(0.62-1.83)
Atrophy†				
Model I[a]	1.24	(0.95-1.62)	1.42	(1.03-1.97)
Model II[b]	1.29	(0.97-1.71)	1.39	(0.98-1.96)

IRR, Incidence rate ratio; CI, Confidence Interval; ICV, Intracranial volume; MMSE, Mini-Mental State Examination
† Highest quartile versus the three lowest quartiles (white matter lesions, >0.08% increase in total white matter lesion volume (% of ICV); atrophy, >1.70% decrease in brain parenchymal fraction)
White matter lesions, lacunar infarcts, and atrophy measures were entered in the same model
[a] Adjusted for age, sex, education and MMSE
[b] Additionally adjusted for physical functioning, antidepressant use, smoking, alcohol intake, body mass index, hyperlipidemia, hypertension and diabetes mellitus

Exclusion of patients with major depressive disorder

Exclusion of patients with major depressive diagnosis (n=35) resulted in similar effect estimates and significance levels (data not shown), except associations of cortical atrophy with appetite disturbance (RR=1.11, 95% CI 0.87-1.41), and progression of WML volume with appetite disturbance (RR=1.28, 95% CI 0.78-2.12) attenuated and were no longer significant.

Exclusion of patients with cortical or large subcortical infarcts

Exclusion of patients with cortical or large subcortical infarcts on MRI (n=87) resulted in similar estimates and significance levels, except associations of lacunar infarcts in deep white matter (RR=1.68, 95% CI 0.74-3.82) and thalamus (RR=1.85, 95% CI 0.65-5.25) with psychomotor retardation attenuated and were no longer statistically significant.

Discussion

In this cohort of patients with symptomatic atherosclerotic disease, we observed that lacunar infarcts in deep white matter tracts were associated with greater motivational as well as mood sumscores. When we differentiated between individual depressive symptoms, most symptoms associated with white matter lesions and lacunar infarcts in the deep white matter were characteristic of motivational problems, while those associated with cortical brain atrophy were more diverse. Furthermore, patients with greatest progression of WML volume were also at increased risk of motivational symptoms.

To our knowledge, this is the first study investigating associations of WML volume, lacunar infarcts and atrophy at different locations with the risk of characteristic depressive symptom profiles. Further, studies examining lesion progression and the risk of depressive symptom profiles have not yet been published. Other strengths include the large number of patients and the extensive information on small-vessel and degenerative MRI changes. Also, the use of volumetric assessment of WML and atrophy provided more precise and objective estimates than visual rating scales [34,35], and enabled us to detect small volume changes over time more accurately.

A limitation of this study is that we did not distinguish other locations of atrophy in more detail, including the prefrontal cortex. In addition, depressive symptoms were assessed with the Patient Health Questionnaire-9 and not with structured interviews. The low overall PHQ-9 score may have narrowed the contrast between patients with depressive symptoms and those without. The large sample size should however be sufficient to detect significant relations between structural changes and depressive symptoms, even if the contrast between subjects was relatively small. Also, we investigated relations of structural brain changes with individual depressive symptoms, irrespective of symptom frequency. Finally, we can not draw firm conclusions regarding the direction of causality between progression of structural changes and depressive symptoms, because depressive symptoms were only assessed at follow-up.

The 'vascular depression' hypothesis postulates that location of cerebrovascular lesions in prefrontal structures or their modulating pathways could predispose to a vulnerability of late-life depression [8,9], with clinical presentation of lack of interest, psychomotor retardation and greater disability. Possible underlying neuropathological mechanisms include the disruption of frontal-subcortical pathways by subcortical ischemic lesions [12], or by a combination of vascular and age-related degenerative disease [10,12].

Direct evidence supporting the hypothesis that disruption of frontal-subcortical pathways by small-vessel or degenerative changes is associated with a motivational symptom profile is scarce, because most studies investigating whether vascular disease is associated with a characteristic depressive symptom profile did not use MRI. One study reported that depressed elderly with clinically defined risk factors for vascular depression showed more psychomotor retardation, and less agitation and guilt feelings than depressed elderly without such risk factors [36]. However, two population-based studies could not demonstrate any significant differences in symptom patterns between depressed subjects with and without vascular risk factors or vascular disease, except for greater overall disability [37,38]. A possible explanation for these discrepancies could be that cerebrovascular lesions directly predispose to an increased vulnerability for depressive symptoms, and that these lesions are not associated with extracerebral atherosclerosis [39].

Only one previous study in community-living elderly distinguished the location of small-vessel changes and individual depressive symptoms [14]. This study suggested that WML volume, located in deep white matter, increased the risk of impaired motivation, concentration and decision making, but lacunar infarcts and atrophy were not assessed. Other MRI studies either investigated associations of small-vessel changes or atrophy with depression sumscores and not with symptom characteristics, or only assessed small-vessel or atrophic severity and not location. For instance, one study reported higher levels of apathy among depressed patients with higher severity of WML or gray matter lesions [15]. In this study, other characteristic symptoms associated with small-vessel lesions could not be identified. Since depressive symptoms were examined within patients with clinical depression, it is possible that the contrast between individual depressive symptoms was much smaller than in subjects not selected on their depression status.

Our findings provide support for a relation between disruption of frontal-subcortical pathways by small-vessel lesions and motivational depressive symptoms, insofar that WML and lacunar infarcts located in projecting deep white matter tracts were associated with several individual symptoms characteristic of motivational problems, which are in agreement with symptoms that have been previously associated with disruption of cognitive/ behavioural circuits (i.e., the anterior cingulate cortex, dorsolateral prefrontal cortex and orbitofrontal cortex) [40]. Additional analyses showed that associations of lacunar infarcts in deep white matter and thalamus with psychomotor retardation were partially explained by concurrent large-vessel disease. In addition to lesion location, greater progression of WML volume increased the risk of mainly motivational symptoms, including anhedonia, concentration problems and psychomotor retardation. These findings indeed suggest that higher WML volume is not only associated with, but could be a preceding mechanism contributing

to an increased risk of motivational depressive symptoms. Interestingly, associations of subcortical small-vessel lesions with motivational symptoms did not change when patients with major depressive disorder were excluded. Although we did not measure apathy, these findings suggest that symptoms associated with disruption of fronto-subcortical pathways could be part of a motivational syndrome that resembles apathy, rather than a 'vascular depression' subtype.

Few subjects (1.9%) in our sample scored below the normal range of global cognitive function (MMSE<24) [27]. In this respect, our population had, on average, normal age-adjusted cognitive performance. Recently, we associated the presence of lacunar infarcts in deep white matter tracts with poorer executive functioning in patients with symptomatic atherosclerotic disease [41]. Our current findings suggest that although poorer executive functioning is associated with psychomotor retardation, it is not an intermediate factor in the pathway between small-vessel lesions in the deep white matter and motivational symptoms.

The controversies in findings from previous studies investigating the 'vascular depression' hypothesis incited the recent debate on the role of cerebral small-vessel disease in the development of depressive symptoms in later life. A recent population-based study found that atherosclerosis was not associated with incident depression, and suggested that depression may contribute, rather than result from, vascular burden, or that both result from a mutual underlying mechanism [42]. However, this study did not use MRI markers of cerebral small-vessel disease. Our findings indicate that it is important to examine location and progression of cerebral small-vessel disease, and to distinguish motivational and mood symptoms rather than investigating depressive sumscores, and suggest that disruption of frontal-subcortical pathways by small-vessel lesions leads to a symptom profile characteristic of motivational problems, also in the absence of major depressive disorder. Additional analyses showed that large-vessel disease could also play a role in these associations. Atrophy was associated with a more mixed pattern of motivational and mood symptoms. In view of the large number of associations investigated in this study, some associations may be due to chance and additional studies are needed to confirm our findings and to further clarify the direction of causation between disruption of fronto-subcortical pathways by small-vessel lesions and motivational symptoms.

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Chapter 5.2

Lacunar infarcts in deep white-matter are associated with a more severe and fluctuating course of depressive symptoms

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Abstract

Objectives

Disruption of frontal-subcortical circuits by cerebral small-vessel disease is thought to predispose to a depression subtype characterized by motivational problems. We examined the influence of lacunar infarcts and white matter lesions (WML) in different brain regions on the severity and course of depressive symptoms during three years follow-up.

Methods

Within the SMART-Medea study, analyses were performed in 650 patients (62±9 years). Volumetric WML measures (deep and periventricular) were obtained with 1.5T MRI at baseline; infarcts in different locations were rated visually. Depressive symptoms were assessed with the Patient Health Questionnaire-9 (range 0-27) at baseline and during 5 follow-up times, and categorized into motivational and mood scores.

Results

Using Generalized Estimating Equation models a relation between lacunar infarcts in deep white-matter and a more severe (mean difference=1.47, 95%CI 0.33-2.60) and fluctuating course (p-value interaction infarcts*time=0.04) of depressive symptoms during follow-up was found, adjusted for age, sex, education, vascular risk and cognition. This relation was primarily driven by motivational symptoms. Lacunar infarcts in lobar white matter or in deep gray matter were not associated with severity or course of depressive symptoms. Deep WML volumes were associated with a more fluctuating but not more severe course of depressive symptoms. Excluding patients with major depressive disorder did not change the results.

Conclusions

During 3 years follow-up motivational symptoms remained higher in patients with lacunar infarcts in deep white-matter, and symptom severity fluctuated over time. This relation was independent of major depression and suggests that these symptoms may be apathy-related rather than depression characteristics.

Introduction

A relation between cerebral small-vessel disease, characterized by lacunar infarcts and white matter lesions (WML) on magnetic resonance imaging (MRI), and depressive symptoms in later life has been well-established [1-4]. The 'vascular depression' hypothesis proposes disruption of frontal-subcortical structures or their connecting pathways as a potential mechanism by which cerebral small-vessel disease may predispose to or precipitate depressive symptoms [5,6]. Clinical manifestations of frontal-subcortical dysfunction comprise motivational symptoms, including anhedonia, psychomotor retardation, lack of energy and executive dysfunction [7]. Although few studies are available, they have indeed found lacunar infarcts and WML in deep white-matter to be associated with motivational rather than mood symptoms in persons with [8] and without major depression [9,10].

Although a relation between cerebral small-vessel disease and depressive symptoms has been found, it remains unclear whether lacunar infarcts and WML may actually cause, maintain or aggravate depressive symptoms or whether both result from mutual underlying mechanisms. Only one study found a relation between greater WML volume at baseline and incident depressive symptoms after two to four years follow-up [11]. Two other studies on the other hand found lacunar infarcts and WML at baseline to be associated with an increase in severity or perseverance of depressive symptoms but not with incident depressive symptoms after one and four years follow-up [12,13], whereas two other studies could not demonstrate any significant relationships between lacunar infarcts and WML at baseline and depressive symptoms after three years [14,15]. A possible explanation for the inconsistencies in longitudinal findings may be that depressive symptoms typically fluctuate in severity over time [16]. Because most studies assessed depressive symptoms only once or few times during follow-up, these fluctuations in the severity of depressive symptoms may explain why the strength of the relationship between cerebral small-vessel disease and depressive symptoms is not constant but differs over time.

Further, it is unknown whether the influence of WML and lacunar infarcts on the course of depressive symptoms is equally important. Although WML and lacunar infarcts are often considered as different expressions of a single underlying disease, i.e. cerebral small-vessel disease, WML and lacunar infarcts have increasingly been shown to be associated with a different clinical prognosis [17].

Finally, so far longitudinal studies have only investigated the association of WML and lacunar infarcts with overall severity of depressive symptoms during follow-up, and did not distinguish whether, in line with the concept of frontal-subcortical dysfunction, these symptoms are primarily characterized by motivational problems.

The aim of this study was first to examine whether lacunar infarcts and WML volume in different brain regions were associated with a more severe and fluctuating course of depressive symptoms, measured 6 times during 3 years follow-up. Second, we examined whether observed associations were primarily driven by underlying motivational or mood symptoms.

Materials and methods

Subjects

Data were used from the SMART-Medea (Memory, depression and aging) study, an ancillary study to the Second Manifestations of ARTerial disease—Magnetic Resonance (SMART-MR) study, intended to investigate brain changes associated with psychosocial vulnerability and stress factors in 710 independently living participants with symptomatic atherosclerotic disease. Details of the design and participants of the SMART-MR and SMART-Medea study have been described elsewhere [18,19]. In brief, between March 2006 and May 2009, patients with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, or an abdominal aortic aneurysm (AAA), and without MRI contraindications, were invited to participate. During a 1-day visit to our medical center, an MRI of the brain, neuropsychological testing, measurements of depression early and later in life, physical examination, blood and urine sampling, risk factors, medical history and functioning were assessed. The SMART-MR and SMART-Medea study were approved by the ethics committee of our institution, and written informed consent was obtained from all participants.

Magnetic Resonance Imaging Protocol

MRI investigation was performed on a 1.5-Tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of a transversal T1-weighted gradient-echo sequence (repetition time (TR)/echo time (TE): 235/2 ms; flip angle, 80º), a transversal T2-weighted turbo spin-echo sequence (TR/TE: 2200/11 ms and 2200/100 ms; turbo factor 12), a transversal T2-weighted fluid attenuating inverse recovery (FLAIR) sequence (TR/TE/inversion time (TI): 6000/100/2000 ms) and a transversal inversion recovery (IR) sequence (TR/TE/TI: 2900/22/410 ms) (field of view 230x230 mm; matrix size, 180x256; slice thickness, 4.0 mm; no gap; 38 slices).

Brain segmentation

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique has been described elsewhere [20,21]. The segmentation program distinguishes cortical gray matter, white matter, sulcal and ventricular cerebrospinal fluid (CSF), and lesions. The results of the segmentation analysis were visually checked for the presence of infarcts and adapted if necessary to make a

distinction between WML and infarct volumes. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, the volumes of WML and infarcts. All volumes cranial to the foramen magnum were included. As a result, the total brain volume includes the cerebrum, brainstem and cerebellum. Total intracranial volume (ICV) was calculated by summing the total brain volume and the volumes of the sulcal and ventricular CSF.

Infarcts and white matter lesions

The whole brain was visually searched for infarcts by a trained investigator and a neuroradiologist. Raters were blinded regarding the history and diagnosis of the patient. Discrepancies in rating were re-evaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3 mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images in order to distinguish them from WML. Dilated perivascular spaces were distinguished from infarcts on the basis of their location, form, and the absence of gliosis. The location, affected flow territory and type were scored for every infarct. Brain infarcts were categorized as cortical infarcts, lacunar infarcts, large subcortical infarcts and infratentorial infarcts. Large subcortical infarcts were sized >15 mm and were not confluent with cortical infarcts. We defined lacunar infarcts as infarcts of 3 to 15 mm in diameter and located in the frontal, parietal, temporal and occipital lobes (defined as lobar white-matter), corona radiata, internal capsule, semioval center (defined as deep white-matter; figure 1), thalamus or basal ganglia (defined as deep gray matter). Infratentorial infarcts were located in the brainstem or cerebellum, irrespective of size. Periventricular lesions were defined as WML adjacent to or within 1 cm of the lateral ventricles in both hemispheres. Deep lesions were located in the deep white matter tracts and may or may not have adjoined periventricular lesions. Volumes of periventricular and deep WML were summed to obtain the total volume of WML. Volumes of WML were normalized for ICV, and expressed as percentage of ICV.

Depressive symptoms

The Patient Health Questionnaire-9 (PHQ-9) [22,23] was used to assess depressive symptoms at baseline. The PHQ-9 assesses the presence of the nine DSM-IV symptoms for major depressive disorder in the past two weeks. Responses are scored on a 4-point Likert scale of 0 to 3, indicating that the participant experienced the symptom “not at all”, “on several days”, “on more than half the days” or “nearly every day”, with higher scores indicating more severe symptoms. According to previously reported classifications [9,24,25], we distinguished motivational (anhedonia, energy loss, concentration problems and psychomotor retardation) and mood profiles (depressed mood, appetite disturbance, feelings of guilt and suicidal thoughts) by counting the positively rated criteria (range 0-12). Sleep disturbance

was not included in either profile [24,25]. Starting in July 2008, the PHQ-9 questionnaire was sent biannually to all participants.

The presence of major depressive disorder according to DSM-IV criteria [26] in the preceding 12 months was assessed at baseline in all participants using the Composite International Depression Interview (CIDI, version 2.1) [27]. The use of antidepressant medication (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors, or Monoamine Oxidase Inhibitors) was assessed through questionnaires.

Assessment of cognitive functioning

Global cognitive functioning was measured with the Mini-Mental State Examination (MMSE) [28]. Executive function was assessed with three tests. The visual elevator test (subtest of the Test of Everyday Attention [29]) is a timed test of 10 trials that measures mental flexibility and shifting of attention. The Brixton Spatial Anticipation test [30] was used to assess the capacity to discover logical rules and mental inhibition and flexibility. The total number of errors made was scored. The Verbal Fluency test (letter A, one minute time frame) was used to assess mental flexibility and employment of strategies. Before calculating the z-scores, the scores of the Visual Elevator test and Brixton Spatial Anticipation test were multiplied by minus one, so that lower scores represented poorer performance. A composite z-score was computed by averaging z-scores of the three subtests.

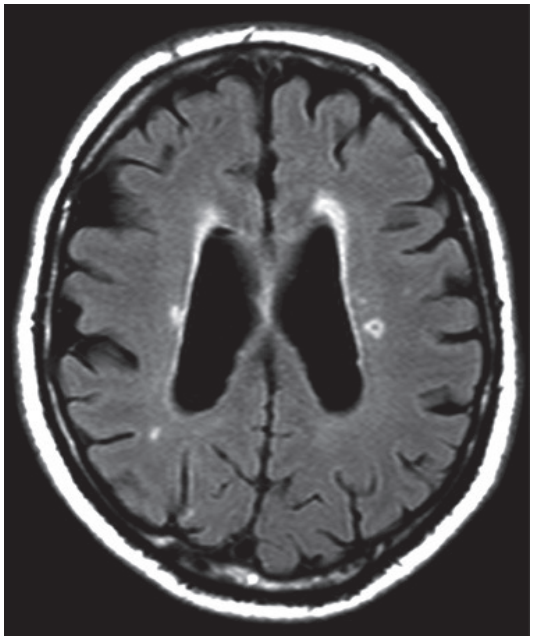

Figure 1 T2-weighted fluid attenuating inverse recovery (FLAIR) image illustrating a lacunar infarct in the deep white-matter tracts in the left hemisphere.

Other variables

During the visit to the medical center, an overnight fasting venous blood sample was taken to determine glucose levels. Height and weight were measured without shoes and heavy clothing, and body mass index (BMI) was calculated (kg/m^2). Systolic and diastolic blood pressures (mm Hg) were measured three times with a sphygmomanometer and averaged. Hypertension was defined as mean systolic blood pressure ≥160 mm Hg, mean diastolic blood pressure ≥95 mm Hg, or self reported antihypertensive drug use. Diabetes mellitus was defined as history of diabetes mellitus, glucose ≥7.0 mmol/L, or self reported use of oral antidiabetic drugs or insulin. Smoking habits and alcohol intake were assessed with questionnaires. Pack-years of smoking was calculated, and alcohol use was categorized into <1 drink per week, 1–20 drinks per week, and >20 drinks per week. Physical health status was assessed with the Physical Component Summary scale of the Short Form-12 (SF-12) [31].

Study sample

Of the 710 patients participating in SMART-Medea, data on MRI variables was missing in 60 patients (no MRI: 44, motion or artefacts: 16), resulting in a total sample of 650 patients.

Data analysis

First, baseline characteristics were calculated for the study population. Then, PHQ-9 scores at baseline were compared between patients without lacunar infarcts and those with lacunar infarcts in different brain regions (deep white-matter, lobar white-matter or deep gray matter) using linear regression analysis with robust standard errors, adjusted for age, sex and education. We then compared underlying motivational and mood scores between patients without lacunar infarcts and patients with lacunar infarcts in different brain regions. Analyses were repeated for deep and periventricular WML volume (% ICV). Because of skewed distributions, WML volume was analyzed as dichotomous variable (highest quartile vs. three lowest quartiles), to compare patients with most severe WML to those with no or minimal WML.

Second, to determine whether lacunar infarcts influenced the course of depressive symptoms over time, Generalized Estimating Equation (GEE) models with robust standard errors were used to investigate associations of lacunar infarcts in different brain regions (as independent variable) with PHQ-9 score (range 0-27) at multiple time points during follow-up (as dependent variable). Time between baseline and repeated PHQ-9 assessments was divided into intervals of six months. Analyses were adjusted for age, sex, education and follow-up time (model 1). In addition, we added the interaction term lacunar infarcts*follow-up time to model 1 to investigate whether lacunar infarcts were associated with a different course of depressive symptoms over time. We additionally adjusted for smoking, alcohol use, BMI,

hypertension and diabetes mellitus in model 2, and for antidepressant use, executive function and total WML volume in model 3. For significant associations, we repeated the analyses using motivational and mood sumscores (range 0-12), respectively, as dependent variable, to examine to what extent the observed relation was driven by motivational symptoms. We repeated all analyses with deep and periventricular WML volume as independent variables.

As a final step, all analyses were repeated after excluding patients with a diagnosis of major depressive disorder (n=43) to investigate whether associations of lacunar infarcts and WML with depressive symptoms were independent of clinical depression.

Table 1 Baseline characteristics of the SMART-Medea cohort (n=650)

Age[¥] (years)	62 ± 9.4
Female gender (%)	119 (19)
Smoking[†] (pack-years)	19 (0-49)
Body mass index[¥] (kg/m^2)	27 ± 3.8
Alcohol use (%)	
- <1 drink per week	98 (15)
- 1-20 drinks per week	474 (74)
- >20 drinks per week	72 (11)
Hypertension (%)	394 (61)
Diabetes mellitus (%)	138 (21)
MMSE[†]	29 (27-30)
Total intracranial volume[¥] (mL)	1458 ± 127
Presence of lacunar infarcts (%)	138 (22)
- Deep white-matter	69 (11)
- Lobar white-matter	47 (7)
- Deep gray matter	72 (11)
Total WML volume[†] (mL)	1.4 (0.4-9.5)
- Deep WML volume	0.5 (0.1-3.7)
- Periventricular WML volume	0.8 (0.2-5.8)
Presence of non-lacunar infarcts (%)	124 (19)
Antidepressant use (%)	50 (8)
Patient Health Questionnaire-9 score (range 0-27)[†]	2 (0-8)
- Motivational sumscore (range 0-12)	1 (0-4)
- Mood sumscore (range 0-12)	0 (0-2)

MMSE, Mini-mental state examination; WML, White matter lesion; PHQ-9, Patient Health Questionnaire-9; [¥] Mean ± SD; [†] Median, (10th percentile-90th percentile)

Results

The mean age of the study sample at baseline was 62±9 years and 19% of the sample was female (table 1). The baseline median PHQ-9 score was 2 (10^{th}-90^{th} percentile, 0-8). The median number of PHQ-9 assessments was 5 (10^{th}-90^{th} percentile, 0-9), during a median follow-up time of 43 months (10^{th}-90^{th} percentile, 24-57). The overall response on the repeated PHQ-9 assessments varied between 85% and 95%.

Patients with lacunar infarcts in deep white-matter had significantly more depressive symptoms at baseline, while lacunar infarcts in lobar white matter or in deep gray matter were not associated with baseline depressive symptoms (table 2). When underlying symptom profiles were distinguished, lacunar infarcts in deep white-matter were predominantly associated with more severe motivational symptoms (table 2).

Table 2 Cross-sectional associations at baseline of lacunar infarcts in total and different brain regions, and depressive symptoms (n=650)

	Lacunar infarcts absent (n=512)*	**Lacunar infarcts deep white-matter (n=69)**	**Lacunar infarcts lobar white-matter (n=47)**	**Lacunar infarcts deep gray matter (n=72)**
	Mean score (SE)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
PHQ-9 score (0-27)	2.75 (0.15)	1.56 (0.43 to 2.70)	0.06 (-1.13 to 1.24)	0.43 (-0.48 to 1.33)
Motivational score (0-12)	1.50 (0.08)	0.95 (0.28 to 1.61)	0.06 (-0.63 to 0.75)	0.22 (-0.30 to 0.74)
Mood score (0-12)	0.64 (0.05)	0.44 (0.00 to 0.88)	0.10 (-0.39 to 0.58)	0.13 (-0.23 to 0.49)

PHQ-9, Patient Health Questionnaire-9; SE, Standard error; CI, Confidence interval

* Reference group; Adjusted for age, sex and education

5.2

Patients with lacunar infarcts in deep white-matter also had significantly more depressive symptoms during the course of follow-up compared to those without lacunar infarcts (mean difference over all follow-up measures: 1.47, 95% CI 0.33 to 2.60) (figure 2a). This association attenuated in models 2 and 3, but remained statistically significant (mean difference 1.14, 95% CI 0.03 to 2.25). Moreover, this difference was not stable but fluctuated over time (p-value interaction lacunar infarcts*time=0.04; figure 2a). When underlying symptom profiles were distinguished, patients with lacunar infarcts in deep white-matter had significantly more severe motivational symptoms during follow-up (mean difference 0.71, 95% CI 0.08 to 1.34) as well as more fluctuations in motivational symptoms over time (p for interaction=0.04; figure 2b). Although patients with lacunar infarcts in deep white-matter showed more fluctuations in mood symptoms over time (p-value interaction lacunar infarcts*time =0.10), no significant differences in overall severity of mood symptoms (mean

difference; 0.32, 95% CI -0.11 to 0.75) were found between patients with and without lacunar infarcts in deep white-matter.

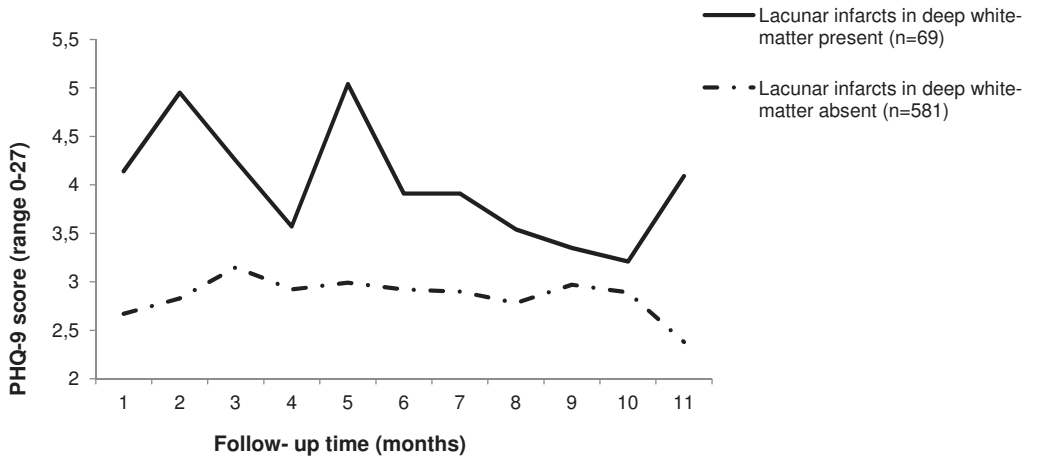

Figure 2a Mean Patient Health Questionnaire-9 (PHQ-9) score during follow-up (range 0-27) for patients with and without lacunar infarcts in the deep white-matter, adjusted for age, sex, education and follow-up time (n=650).

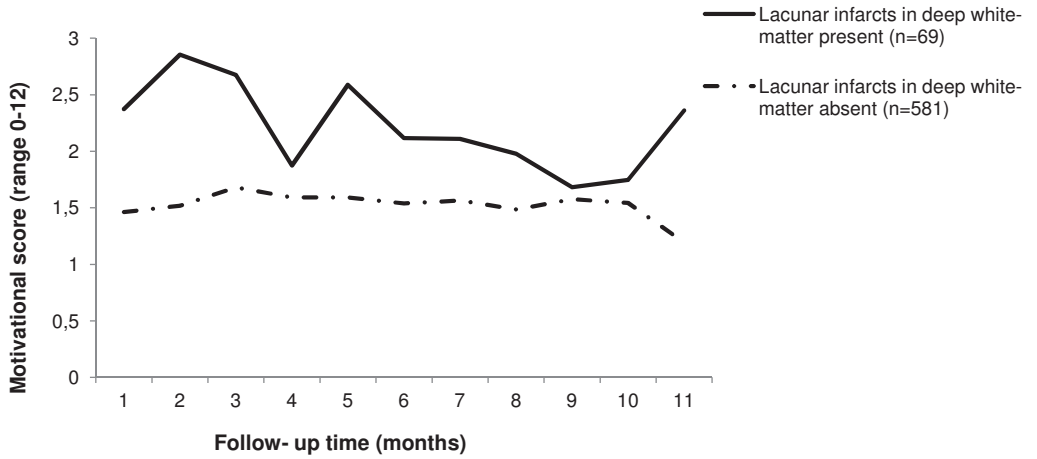

Figure 2b Mean motivational score during follow-up (range 0-12) for patients with and without lacunar infarcts in the deep white-matter, adjusted for age, sex, education and follow-up time (n=650).

No significant differences in the severity or course of depressive symptoms during follow-up were found between patients with and without lacunar infarcts in lobar white-matter (mean difference; -0.03, 95% CI -1.20 to 1.14; p-value interaction lacunar infarcts*time=0.76) or deep gray matter (mean difference; 0.30, 95% CI -0.61 to 1.22; p-value interaction lacunar infarcts*time=0.11).

White matter lesions in deep or periventricular regions were not associated with depressive symptoms, or with underlying motivational or mood symptoms at baseline (table 3). Also, patients in the highest quartile of deep or periventricular WML volume did not differ in the severity of depressive symptoms during follow-up (mean difference 0.09, 95% CI -0.53 to 0.70; B=0.32, 95% CI -0.34 to 0.98 respectively). However, patients with most severe deep WML had a significantly different course of depressive symptoms during follow-up (p-value interaction WML*time=0.04), with more fluctuations (figure 3) compared to those with few or no deep WML. When underlying motivational and mood symptoms were distinguished, no significant differences in the severity or course of motivational (mean difference 0.08, 95% CI -0.27 to 0.43; p-value interaction WML*time=0.30) or mood symptoms during follow-up (mean difference 0.05, 95% CI -0.19 to 0.29; p-value interaction WML*time=0.25) were found between patients in the highest quartile of deep WML volume and those in the lowest quartiles.

Table 3 Cross-sectional associations at baseline of white matter lesion volume in total and different brain regions, and depressive symptoms (n=650)

	Three lowest quartiles of WML volume (n=474)*	**Highest quartile of deep WML volume (n=174)†**	**Highest quartile of periventricular WML volume (n=176)†**
	Mean score (SE)	Mean difference (95% CI)	Mean difference (95% CI)
PHQ-9 score (0-27)	2.69 (0.15)	0.16 (-0.45 to 0.78)	0.43 (-0.24 to 1.10)
Motivational score (0-12)	1.47 (0.09)	0.15 (-0.20 to 0.50)	0.29 (-0.10 to 0.68)
Mood score (0-12)	0.61 (0.06)	0.04 (-0.21 to 0.28)	0.21 (-0.05 to 0.46)

WML, White matter lesion; PHQ-9, Patient Health Questionnaire-9; SE, Standard error; CI, Confidence interval
† Defined as ≥0.08% deep WML volume (% ICV); ≥0.15% periventricular WML volume (% ICV)
* Reference group; Adjusted for age, sex and education

5.2

Excluding patients with major depressive disorder (n=43) did not materially change the effect estimates or significance levels (data not shown).

Discussion

In this cohort of patients with symptomatic atherosclerotic disease, our main finding was that the presence of lacunar infarcts in deep white-matter was associated with more depressive symptoms over the course of three years follow-up, and that these symptoms were mainly driven by motivational problems. Moreover, the severity of motivational problems in these patients was not stable but fluctuated over time.

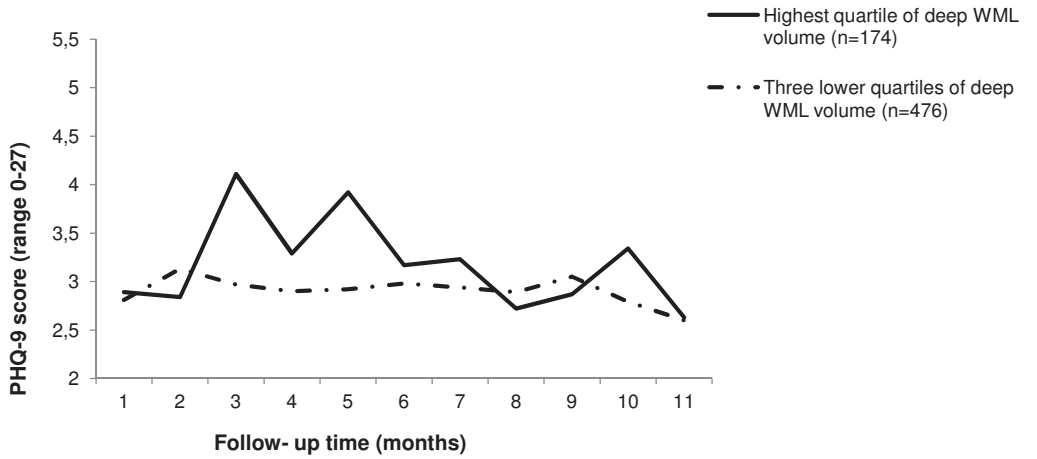

Figure 3 Mean Patient Health Questionnaire-9 (PHQ-9) score during follow-up (range 0-27) for patients in the highest quartile vs. the three lowest quartiles of deep white matter lesion (WML) volume (% of intracranial volume), adjusted for age, sex, education and follow-up time (n=650).

Before we interpret our findings, several strengths and limitations have to be considered. Strengths of our study include the large sample size, the frequent assessments of depressive symptoms with relatively short intervals during three years follow-up, and the high response rates at the follow-up exams. Other strengths are the extensive information on location of lacunar infarcts, automated assessment of WML volumes, and measures of cardiovascular risk factors for which we could adjust in our analyses. A limitation of our study is that we did not have follow-up MRI and therefore could not investigate the influence of new lacunar infarcts and progression of WML on the course of depressive symptoms during follow-up. Further, the relatively low PHQ-9 scores may have led to a decreased contrast in depressive symptom severity, and may have contributed to an underestimation of the observed associations. Finally, although deep and periventricular WML volumes were distinguished, underlying brain regions could not be assessed in greater detail.

Different studies tried to clarify the direction of causation between cerebral small-vessel disease and depressive symptoms. One of these found greater WML volume at baseline to be associated with the risk of incident depressive symptoms after four years follow-up [11], suggesting that WML may be a causal mechanism leading to depressive symptoms. Others could however not demonstrate this relation, and either found an association of lacunar infarcts and WML at baseline with an increase in the severity or perseverance of depressive symptoms after one and four years [12,13] or could not demonstrate any significant relationships [14,15]. We found not only a cross-sectional relationship between lacunar infarcts in deep white-matter and increased depression scores, but also that the influence of these lacunar infarcts on depressive symptoms continued during three years follow-up. Although we did not

examine whether lacunar infarcts actually preceded depressive symptoms, our findings do suggest that lacunar infarcts in deep-white matter are associated with a perseverance of depressive symptoms during three years follow-up, characterized by repeated episodes of exacerbations in the severity of depressive symptoms. Our findings suggest that these pronounced fluctuations in the severity of depressive symptoms in persons with lacunar infarcts in deep white-matter tracts may also partially explain the inconsistencies in the existing literature. As may be seen in figure 2a, the difference in depression scores between baseline and follow-up in persons with lacunar infarcts in deep white-matter strongly depends on the timing of both measurements, particularly when only one or few follow-up measurements are used.

The 'vascular depression' hypothesis proposed disruption of frontal-subcortical circuits as a mechanism by which lacunar infarcts and WML may predispose to depressive symptoms [5,6]. Motivational problems are characteristic features of frontal-subcortical dysfunction [32,33], and have therefore been proposed as dominant features of 'vascular depression' [34]. Previous studies have shown that patients with 'vascular depression' show a weaker response to pharmacological treatment [35], with lower remission rates and more and longer hospitalizations compared to depressed persons without cerebral small-vessel disease [36-38]. In line with the 'vascular depression' hypothesis, we found that the depressive symptoms associated with lacunar infarcts in deep white-matter were predominantly characterized by motivational problems. Nevertheless, an important difference was that the relation between lacunar infarcts in deep white-matter and motivational symptoms was independent of major depressive disorder. This finding suggests that the motivational symptoms associated with lacunar infarcts are not necessarily part of (vascular) depression, but reflect a broader category of apathy-related symptoms irrespective of depression. Because apathy requires a different pharmacological approach than depression and symptoms may worsen with recommended antidepressant treatment [35], this may perhaps also explain the weaker response to antidepressant medication in these patients.

Because lacunar infarcts and WML are thought to be different manifestations of a single underlying disease, i.e. atherosclerosis, it may have been expected to find a similar influence of lacunar infarcts and WML on the course of depressive symptoms. Nevertheless, we could not demonstrate a relation between deep WML and the severity of depressive symptoms during three years follow-up. A possible explanation may be that we distinguished deep and periventricular WML volume. Because recent studies found the relation between WML and depressive symptoms to be primarily driven by WML in the frontal lobe [39], the combination of WML in different lobes into deep WML may have created insufficient contrast. An alternative explanation for the finding that lacunar infarcts in deep white-matter tracts

have a stronger influence on the severity of depressive symptoms than WML, may be that cavitation of a lacunar infarct on brain MRI occurs relatively late in the disease process [40] and therefore may reflect a more severe and advanced state of cerebral small-vessel disease.

In conclusion, we observed that the presence of lacunar infarcts in deep white-matter was associated with more severe and a more fluctuating course of motivational symptoms during three years follow-up. The finding that these symptoms were not stable but fluctuated over time, emphasizes the importance of repeated measurements of depressive symptoms during follow-up. Although our findings may be in line with the concept of disruption of frontal-subcortical circuits, our results suggest that the motivational symptoms associated with lacunar infarcts in deep white-matter may be apathy-related symptoms rather than (vascular) depression characteristics.

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Chapter 6

Brain volume, cerebral small-vessel disease and apathy

Chapter 6.1

Structural MRI correlates of apathy-related symptoms in a large population-based cohort of older persons without dementia. The AGES-Reykjavik Study

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Abstract

Objectives

In dementia, apathy commonly occurs and is associated with structural brain abnormalities. Although apathy is also common in non-demented persons, its association with brain changes is unclear. We examined whether apathy-related symptoms were associated with brain volumes, white matter lesions (WML) and infarcts in different brain regions in a population-based cohort of older persons without dementia.

Methods

Within the AGES-Reykjavik Study, cross-sectional analyses were performed in 4354 non-demented subjects (76±5 years). The Geriatric Depression Scale-15 was used to distinguish apathy-related (range 0-3) and depressive symptoms (range 0-12). Total and regional brain volumes and total WML volume were estimated on 1.5T MRI using an automated segmentation programme; WML load in different brain regions was calculated using a semi-quantitative scale; infarcts were rated visually. Regression analyses were adjusted for age, sex, education, intracranial volume, vascular risk, gait speed and antidepressants.

Results

In the cohort, 4% had 2 or more depressive symptoms only; 35% had 2 or more apathy-related symptoms only; and 14% had a combination of apathy-related and depressive symptoms. Compared to those without symptoms, persons with only apathy-related symptoms had smaller gray matter volumes in all lobes (mean overall difference in gray matter volume -4.18 mL, 95%CI -6.81 to -1.55); and were at increased risk of greater frontal WML load (OR=1.18, 95%CI 0.99-1.41). Persons with a combination of apathy-related and depressive symptoms had significantly smaller gray as well as white matter volumes in all lobes, smaller striatum, hippocampus complex and thalamus volumes, and an increased risk of greater frontal WML load. Excluding participants with major depression did not change the associations.

Conclusions

In this general older population without dementia, apathy-related symptoms, with or without depression, are very common and are associated with an increased WML load in the frontal region, but also with a more diffuse and widespread loss of gray matter volume. These findings suggest that not only vascular pathology contributes to apathy, but also neurodegeneration.

Introduction

Late-life depression has been linked to different etiological pathways [1], including cerebral small-vessel disease [2,3]. The most common manifestation of cerebral small-vessel disease on brain magnetic resonance imaging (MRI) is the presence of white matter lesions (WML) [4]. According to the 'vascular depression' hypothesis, disruption of prefrontal cortex-basal ganglia circuits, leading to impaired nerve conduction in emotion-regulating brain regions may be an underlying mechanism by which WML predispose to late-life depression [5,6].

Symptoms associated with dysfunction of frontal-subcortical circuits are primarily characterized by motivational problems, including anhedonia, energy loss, psychomotor retardation and executive dysfunction, and have therefore been proposed as characteristic features of 'vascular depression' [7,8]. Considering the great overlap in symptom characteristics, these motivational problems may however also be manifestations of apathy [9]. Because most studies investigating the 'vascular depression' hypothesis did not assess apathy [10,11], the relative contribution of apathy-related symptoms to the relation between cerebral small-vessel disease and clinically relevant depressive symptoms is unknown.

Apathy is primarily defined as a syndrome of loss of motivation, and is characterized by symptoms of diminished initiation, low social engagement, indifference, poor persistence, psychomotor retardation and energy problems [9,12]. Despite the overlap in motivational symptoms, apathy differs in prognosis and pharmacological treatment [13,14], and can occur independent of depression [15]. Another important difference between apathy and depression is that apathy is not characterized by symptoms of depressed mood, one of the dominant features of depression [16].

Apathy is one of the most common neuropsychiatric symptoms in patients with cognitive impairment and Alzheimer's disease [17,18], and has not only been associated with more severe WML in the frontal lobe [19,20] but also with atrophy of the frontal gray matter, striatum and thalamus in these patients [21-23]. It is however unclear whether these findings may also be generalized to non-demented persons, since in patients with Alzheimer's disease these structural changes are commonly present on brain MRI and are strongly related to cognitive performance [24]. Although apathy also commonly occurs in the general older population [17], little is known on the role of cerebral small-vessel disease and atrophy on apathy symptoms in these persons.

The aim of this study was first to examine the relative contribution of apathy-related symptoms to clinically relevant depressive symptoms in a large population-based cohort of non-demented older persons. Second, we investigated to what extent apathy-related

symptoms are associated with WML, atrophy and the presence of infarcts in brain regions involved in the regulation of emotions in non-demented older persons. Third, we examined whether observed associations were independent of the presence of major depressive disorder to investigate whether these symptoms may be expressions of apathy or depression characteristics.

Materials and methods

Participants

Study participants came from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, a single center prospective population-based cohort study originating from the Reykjavik Study, as fully described elsewhere [25]. Briefly, the Reykjavik Study was initiated in 1967 and included men and women who were born between 1907 and 1935 and were living in Reykjavik. From 2002 through 2006, 5764 persons, randomly chosen from survivors of the Reykjavik Study, were examined for the AGES-Reykjavik Study. The AGES-Reykjavik Study aims to investigate the contribution of genetic susceptibility, environmental factors, and gene-environment interaction to clinical and subclinical disease among elderly people. As part of comprehensive assessments at the Reykjavik research center participants answered questionnaires and underwent clinical examinations, had blood drawn, cognitive testing, and brain MRI. The AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Icelandic Data Protection Authority, Iceland, and by the Institutional Review Board for the National Institute on Aging, National Institutes of Health, USA. Written informed consent was obtained from all participants.

MRI protocol

All participants without contraindications were eligible for brain MRI scan on a study-dedicated 1.5T Signa Twinspeed system (General Electric Medical Systems, Waukesha, WI). The image protocol included an axial T1-weighted 3-dimensional spoiled gradient echo sequence (time to echo (TE) 8 ms; repetition time (TR) 21 ms; flip angle (FA) 30°; field of view (FOV) 240 mm; matrix 256x256; slice thickness 1.5 mm); a fluid attenuated inversion recovery (FLAIR) sequence (TE 100 ms; TR 8000 ms; inversion time 2000 ms; FA 90°; FOV 220 mm; matrix 256x256); a proton density/T2-weighted fast spin echo (FSE) sequence (TE1 22 ms; TE2 90 ms; TR 3220 ms; echo train length 8; FA 90°; FOV 220 mm; matrix 256x256); and a T2*-weighted gradient echo type echo planar (GRE-EPI) sequence (TE 50 ms; TR 3050 ms; flip angle (FA) 90°; field of view (FOV) 220 mm; matrix 256x256). The FLAIR, PD/T2 and T2* sequences were acquired with 3 mm thick interleaved slices. All images were acquired to give full brain coverage and slices were angled parallel to the anterior commissure-posterior commissure line.

Brain volumes, white matter lesions and infarcts

The intracranial volume and the brain parenchyma compartments were segmented automatically with an AGES-Reykjavik Study modified algorithm based on the Montreal Neurological Institute pipeline [26]. The pipeline combined the use of a probabilistic atlas, based on a sample of the AGES cohort (n=314), and a multispectral tissue segmentation method. Details of the protocols for the segmentation of gray and white matter regions and WML have been described in detail elsewhere [27]. Volumes of gray matter, normal white matter, WML and cerebrospinal fluid were estimated for each subject, and summed to obtain total intracranial volume (ICV). In addition, trained radiographers scored the location of subcortical WML in the frontal, occipitoparietal, and temporal lobes using the Achten scale [28]. WML were defined as visible hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery images. The scale provides a semiquantitative 'volumetric' estimation for WML load by taking into account the size and number of lesions in the subcortical area. Cerebral infarcts, identified by trained radiographers, were defined as defects in the brain parenchyma with associated hyperintensity on T2 and FLAIR images with maximal diameter of at least 4 mm. For infarcts in the cerebellum and brainstem or infarcts with cortical involvement, no size criterion was required.

Apathy-related and depression measures

The 15-item Geriatric Depression Scale (GDS-15) was used to assess depressive symptoms, and the generally used cut-off score ≥6 was used to indicate the presence of clinically relevant depressive symptoms [29]. Each of the 15 items can be scored as present or absent, and the total score thus ranges from 0 to 15 points. In line with previous factor analyses, an apathy score was calculated consisting of the sum of 3 apathy-related items ('Have you dropped many of your activities and interests?', 'Do you prefer to stay at home, rather than going out and doing new things?' and 'Do you feel full of energy?'; range 0-3 points) [30-33]. The remaining 12 items were summed to obtain a depression score (range 0-12 points) [30,31]. Apathy-related symptoms were defined present if 2 of the 3 apathy-related items were present, and depressive symptoms were defined present if 2 or more of the 12 depression items were present [30,34]. We made 4 mutually exclusive groups: no apathy-related and no depressive symptoms; depressive symptoms only; apathy-related symptoms only; and both apathy-related and depressive symptoms.

In addition, all participants underwent the MINI International Neuropsychiatric interview [35] to assess the presence of major depressive disorder according to DSM-IV criteria in the preceding two weeks and in the past [36]. Participants were eligible for the MINI interview if they had a score ≥6 on the GDS-15, or if they had a GDS-15 score of 4 or 5 and reported occurrences of anxiety, or if they ever had a doctor diagnosis of depression or ever used antidepressant medications as assessed from medication vials brought to the clinic.

Assessment of dementia

Dementia ascertainment was a 3-step protocol as described previously [25]. In brief, all participants were screened using the Mini-Mental State Examination (MMSE) [37] and the Digit Symbol Substitution test [38]. Those with positive screen results were administered a diagnostic battery of neuropsychological tests and, among them, those with positive screen results were examined by a neurologist and a proxy interview was administered regarding medical history, social, cognitive, and daily functioning changes of the participant. A consensus diagnosis according to international guidelines [36] was made by a panel that included a geriatrician, neurologist, neuropsychologist and neuroradiologist.

Other variables

Age, sex, education (categorized into primary, secondary, and college/university education), smoking history (ever vs. never), history of coronary artery disease (present vs. absent) and alcohol intake (type and number of units per day) were assessed via questionnaires. Total alcohol intake (grams) was calculated as the number of units times 14 grams (one unit). Body mass index (BMI) was calculated as measured weight (kg) divided by height (m) squared. Systolic and diastolic blood pressure was measured with a standard mercury sphygmomanometer and the mean of two measurements was calculated. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of antihypertensive medication. Diabetes mellitus was defined as self-reported history of diabetes, use of blood glucose-lowering drugs or fasting blood glucose level ≥7.0 mmol/L. Gait speed was evaluated as the time in seconds needed to walk 6m at usual pace as a measure of overall mobility [39].

Analytical sample

Of the 5764 persons included, 761 had no MRI (contraindications n=279, refusals n=284, home visit n=198) and were excluded. Of the 5003 persons with MRI, 389 were excluded due to image acquisition artefacts and registration failures in post-processing. From these, all participants with a dementia diagnosis (n=260) were excluded, leaving 4354 participants for analysis.

Data analysis

We used multiple imputation (AregImpute) [40] (10 datasets) to address missing values in the study sample of 4354 persons, using the statistical programme R (version 2.13.1). Data were analyzed using PASW version 17.0 (Chicago, III, USA), by pooling the 10 imputed datasets. First, baseline characteristics were compared between the 4 mutually exclusive categories of apathy-related and depressive symptoms (with no apathy-related and no depressive symptoms as reference category).

Then, to confirm a relation between the generally used definition of clinically relevant depressive symptoms and brain volumes, the association of the cut-off ≥6 on the GDS-15 and total brain volume, including total gray and normal white matter, was estimated using linear regression analysis. Adjustments were made for age, sex, education and ICV (model 1), and additionally for smoking history, alcohol intake, BMI, hypertension, diabetes mellitus, gait speed, history of coronary artery disease, infarcts on MRI and antidepressant use (model 2).

Next, to investigate the relative contributions of underlying apathy-related and depressive symptoms, analyses were repeated with the 4 categories of apathy-related and depressive symptoms as independent variables. Also, to investigate whether the combined effect of apathy-related and depressive symptoms exceeded their additive effects an interaction term apathy*depressive symptoms was added to model 2. We repeated the analyses after distinguishing gray and white matter volumes in different brain regions (frontal, temporal and occipitoparietal regions, striatum, hippocampus complex and thalamus) as dependent variables to investigate which brain structures were most strongly associated with apathy-related symptoms.

We repeated all analyses with WML volume as dependent variable. Total WML volume was natural log transformed to obtain a normal distribution. Semi-quantitative measures of WML load in different brain regions (frontal, temporal and occipitoparietal lobes) were dichotomized into the highest quintile vs. the four lowest quintiles, and logistic regression analysis was used to examine associations of apathy-related and depressive symptoms (as independent variables) with WML load in different brain regions (as dependent variables). Adjustment for covariates was as described above. In addition, analyses were repeated using logistic regression analysis with cortical and subcortical infarcts (present vs. absent) in different brain regions (frontal, temporal and occipitoparietal regions, striatum and thalamus) as dependent variables. Adjustment for covariates was as described above.

We repeated all analyses after excluding participants with a lifetime diagnosis of major depressive disorder (n=189).

Results

The mean age of the study population was 76±5 years, 59% was female, and 6% scored above the cut-off ≥6 on the GDS-15. Forty-seven percent of the population had no symptoms; 4% had 2 or more depressive symptoms only; 35% had 2 or more apathy-related symptoms only; and 14% had a combination of depressive and apathy symptoms. Of the persons with apathy-related symptoms alone, 0% scored above the GDS-15 cut-off, and only 44% did so in the group with both apathy-related and depressive symptoms (table 1). In the total cohort, apathy-related symptoms were most frequently reported, with each symptom ranging from 38% to 58%, and depressive symptoms ranging from 1% to 15% (supplementary table 1).

Table 1 Baseline characteristics of the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, stratified to the presence of apathy-related and depressive symptoms (n=4354)

	Total sample (n=4354)	No symptoms (n=2055)*	Depressive symptoms (n=191)	Apathy-related symptoms (n=1505)	Apathy-related and depressive symptoms (n=603)
Age (years)†	76 ± 5.4	75 ± 5.1	76 ± 5.2	77 ± 5.5	77 ± 5.5
Female sex (%)	2548 (59)	1159 (56)	119 (62)	890 (59)	380 (63)
Education (%):					
- Primary	986 (23)	411 (20)	43 (23)	349 (23)	184 (31)
- Secondary	2167 (50)	1026 (50)	101 (53)	753 (50)	287 (48)
- College	707 (16)	349 (17)	24 (13)	241 (16)	92 (15)
- University	494 (11)	268 (13)	23 (12)	163 (11)	40 (7)
Body mass index (kg/m^2)†	27 ± 4.3	27 ± 4.2	27 ± 3.9	27 ± 4.5	27 ± 4.5
Smoking (%)	2475 (57)	1097 (53)	109 (57)	901 (60)	368 (61)
Alcohol (grams per week)‡	3 (0-40)	3 (0-40)	3 (0-40)	3 (0-40)	2 (0-33)
Hypertension (%)	3491 (80)	1612 (78)	142 (74)	1242 (83)	495 (82)
Diabetes (%)	485 (11)	224 (11)	16 (8)	171 (11)	74 (12)
Gait speed (seconds)‡	6 (5-9)	6 (5-8)	6 (5-8)	7 (5-9)	7 (5-10)
Coronary artery disease (%)	890 (20)	385 (19)	41 (22)	322 (21)	135 (22)
MMSE‡	27 (24-30)	28 (24-30)	27 (23-29)	27 (24-29)	27 (23-29)
Presence of cerebral infarct (%)	1317 (30)	541 (26)	46 (24)	522 (35)	208 (35)
Antidepressant use (%):	643 (15)	210 (10)	34 (18)	238 (16)	161 (27)
- TCA	144 (3)	50 (3)	7 (4)	45 (3)	43 (7)
- SSRI	375 (9)	113 (6)	24 (13)	145 (10)	92 (15)
- Other	176 (4)	60 (3)	6 (3)	65 (4)	46 (8)
GDS-15 score:					
- Overall score‡	2 (0-5)	1 (0-2)	3 (2-5)	3 (2-4)	5 (4-9)
- Score ≥6 (%)	278 (6)	0 (0)	15 (8)	0 (0)	263 (44)

MMSE, Mini-Mental State Examination; TCA, Tricyclic Antidepressant; SSRI, Selective Serotonin Reuptake Inhibitor; GDS-15, 15-item Geriatric Depression Scale; SD, Standard Deviation

* Reference category

† Mean ± standard deviation; ‡ Median (10^{th}-90^{th} percentile)

Percentage of missing values: education: 0.8%, smoking: 0.1%, alcohol use: 0.5%, gait speed: 2.2%, depressive symptoms: 5.2%, antidepressant use: 8.9%, all other variables: 0.0 %

The GDS-15 ≥6 was significantly associated with smaller total brain (model 2, mean difference -10.62 mL, 95% CI -16.74 to -4.64), total gray matter (mean difference -5.41 mL, 95% CI -10.33 to -0.62) and total normal white matter volume (mean difference -5.88 mL, 95% CI -9.06 to -2.68). Also, GDS-15 ≥6 was associated with significantly greater total WML

volume (mean difference 1.13 mL, 95% CI 1.02 to 1.25). No significant associations with the presence of cortical or subcortical infarcts were found (data not shown).

Categories of apathy-related and depressive symptoms, and brain volumes

When the contribution of apathy-related and depressive symptoms was distinguished, depressive symptoms alone were not significantly associated with total brain, total gray matter, or total normal white matter volume after adjustment for covariates (table 2). Also when different brain regions were distinguished, no significant associations were observed (table 3).

Apathy-related symptoms alone were, however, significantly associated with smaller total brain, total gray matter, and total normal white matter volumes (table 2). Part of this association was explained by covariates, but all associations remained significant in the fully adjusted model. When different brain regions were distinguished, apathy-related symptoms alone were significantly associated with smaller gray matter volumes in frontal, temporal and occipitoparietal regions (table 3).

Persons with both apathy-related and depressive symptoms also had significantly smaller total brain, total gray matter, and normal total white matter volumes (table 2). When different brain regions were distinguished, apathy-related plus depressive symptoms were significantly associated with smaller gray matter and smaller white matter volumes in frontal, temporal and occipitoparietal regions, striatum, hippocampus complex and thalamus. Furthermore, the combined effect of apathy-related and depressive symptoms on frontal white-matter volume and volumes of striatum, hippocampus complex and thalamus was significantly greater than their additive effects (table 3).

Categories of apathy-related and depressive symptoms, and white matter lesion volume

Depressive symptoms alone were not associated with total WML volume (table 2). Also when different brain regions were distinguished, no significant associations were observed (figure 1).

Apathy-related symptoms alone were significantly associated with greater total WML volume (table 2). Additional adjustment for covariates somewhat attenuated this effect. When different brain regions were distinguished, apathy-related symptoms alone were significantly associated with an increased risk of greater WML load in the frontal lobe but not in other brain regions (figure 1). Additional adjustment for covariates somewhat attenuated this effect (OR=1.18, 95% CI 0.99-1.41).

Persons with both apathy-related and depressive symptoms also had significantly greater total WML volume (table 2). When different brain regions were distinguished, they had a significantly increased risk of greater WML load in the frontal lobe, and to a lesser extent in the temporal lobe (figure 1). Additional adjustment for covariates somewhat attenuated these effects (OR=1.29, 95% CI 1.02-1.65; OR=1.14, 95% CI 0.90-1.45 respectively).

Table 2 Associations of apathy-related and depressive symptoms as independent, and quantitative measures of total brain, gray and white matter, and white matter lesion volumes as dependent variables (n=4354)

	Overall (n=4354)	**No symptoms (n=2055)***	**Depressive symptoms (n=191)**	**Apathy-related symptoms (n=1505)**	**Apathy-related and depressive symptoms (n=603)**
	Unadjusted total volume (mL)	Mean volume (SE)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
Total brain volume	1084 ± 80†				
- Model 1		1088 (1.09)	-5.16 (-12.44 to 2.13)	-9.26 (-12.56 to -5.95)	-21.36 (-25.87 to -16.85)
- Model 2		1086 (1.08)	-3.10 (-10.30 to 4.14)	-5.17 (-8.43 to -1.88)	-13.12 (-17.76 to -8.56)
Gray matter volume	676 ± 63†				
- Model 1		681 (0.89)	-5.17 (-11.11 to 0.76)	-7.65 (-10.34 to -4.96)	-15.43 (-19.12 to -11.76)
- Model 2		679 (0.87)	-2.82 (-8.60 to 2.97)	-4.18 (-6.81 to -1.55)	-8.42 (-12.15 to -4.78)
White matter volume	386 ± 48†				
- Model 1		389 (0.58)	-1.77 (-5.63 to 2.10)	-4.45 (-6.20 to -2.70)	-10.52 (-12.90 to -8.12)
- Model 2		388 (0.57)	-1.24 (-5.04 to 2.57)	-2.28 (-4.00 to -0.55)	-6.90 (-9.32 to -4.48)
White matter lesion volume	13.5 (4.3-44.3)‡				
- Model 1		12.38 (0.24)	1.04 (0.92 to 1.18)	1.14 (1.08 to 1.21)	1.27 (1.18 to 1.38)
- Model 2		12.82 (0.23)	1.01 (0.90 to 1.15)	1.06 (1.00 to 1.12)	1.14 (1.05 to 1.23)

* Reference category

† Mean ± standard deviation; ‡ Median (10^{th}-90^{th} percentile)

Model 1: Adjusted for age, sex, education and intracranial volume

Model 2: Additionally adjusted for smoking, alcohol use, body mass index, hypertension, diabetes mellitus, gait speed, coronary artery disease, cerebral infarcts on MRI and antidepressant use

Table 3 Associations of apathy-related and depressive symptoms as independent, and quantitative measures of gray and white matter volumes in different brain regions as dependent variables (n=4354)

	Overall (n=4354)	No symptoms (n=2055)*	Depressive symptoms (n=191)	Apathy-related symptoms (n=1505)	Apathy-related and depressive symptoms (n=603)
	Unadjusted total volume (mL)†	Mean volume (SE)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
Frontal:					
- Gray matter	213 ± 22.4	215 (0.33)	-1.25 (-3.50 to 0.97)	-1.74 (-2.77 to -0.74)	-3.26 (-4.72 to -1.87)
- White matter	137 ± 18.2	137 (0.24)	0.59 (-1.02 to 2.17)	-0.24 (-0.97 to 0.48)	-1.73 (-2.76 to -0.73)‡
Temporal:					
- Gray matter	128 ± 13.2	129 (0.19)	-0.57 (-1.85 to 0.71)	-1.07 (-1.65 to -0.49)	-1.93 (-2.75 to -1.13)
- White matter	63 ± 8.6	63 (0.12)	-0.25 (-1.01 to 0.53)	-0.11 (-0.45 to 0.25)	-0.70 (-1.18 to -0.20)
Occipitoparietal:					
- Gray matter	173 ± 19.2	174 (0.31)	-1.20 (-3.25 to 0.86)	-1.14 (-2.07 to -0.21)	-1.27 (-2.60 to 0.01)
- White matter	124 ± 16.3	125 (0.22)	-0.75 (-2.22 to 0.73)	-0.66 (-1.33 to 0.02)	-1.66 (-2.60 to -0.72)
Striatum	20.2 ± 2.3	20.2 (0.05)	0.09 (-0.21 to 0.39)	0.02 (-0.11 to 0.16)	-0.22(-0.41 to -0.03)‡
Hippocampus complex	10.4 ± 1.2	10.5 (0.02)	0.01 (-0.12 to 0.15)	-0.03 (-0.09 to 0.03)	-0.18 (-0.27 to -0.10)‡
Thalamus	15.1 ± 1.4	15.1 (0.02)	0.00 (-0.15 to 0.15)	-0.05 (-0.12 to 0.01)	-0.20 (-0.30 to -0.11)‡

* Reference category

† Mean ± standard deviation; ‡ P-value for interaction apathy-related*depressive symptoms ≤0.10

Adjusted for age, sex, education, intracranial volume, smoking, alcohol use, body mass index, hypertension, diabetes mellitus, gait speed, coronary artery disease, cerebral infarcts on MRI and antidepressant use

Categories of apathy-related and depressive symptoms, and brain infarcts

Depressive symptoms alone were not associated with the presence of cortical or subcortical infarcts (figure 2). Also when different brain regions were distinguished, no significant associations were observed (supplementary table 2).

Apathy-related symptoms alone were significantly associated with an increased risk of cortical and subcortical infarcts (figure 2). Additional adjustment for covariates somewhat attenuated these effects (OR=1.41, 95% CI 1.11-1.77; OR=1.25, 95% CI 0.96-1.51 respectively). When different brain regions were distinguished, apathy-related symptoms alone were associated with an increased risk of cortical infarcts in frontal and occipitoparietal regions, and infarcts in the thalamus (supplementary table 2).

Persons with both apathy-related and depressive symptoms also had an increased risk of cortical and subcortical infarcts (figure 2). Additional adjustment for covariates somewhat attenuated these effects (OR=1.40, 95% CI 1.02-1.91; OR=1.34, 95% CI 0.96-1.75 respectively). When different brain regions were distinguished, they had an increased risk of cortical infarcts in frontal and occipitoparietal regions (supplementary table 2).

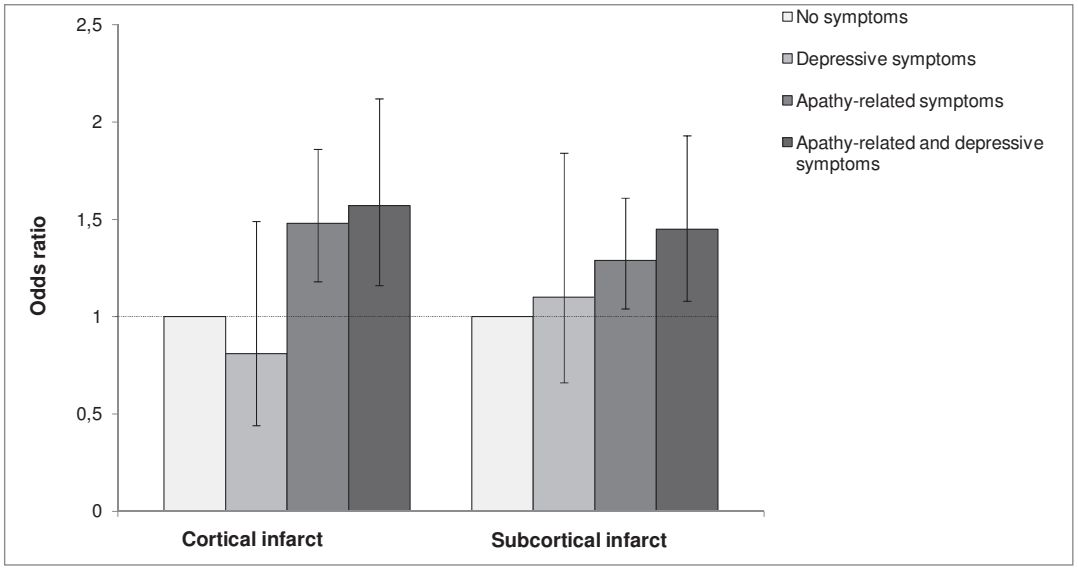

Figure 1 Odds ratios of having high white matter lesion load (highest quintile vs. the four lowest quintiles) in different brain regions for categories of apathy-related and depressive symptoms (with no apathy-related and no depressive symptoms as reference category), adjusted for age, sex, education and intracranial volume. Error bars indicate 95% confidence intervals.

Excluding participants with a lifetime diagnosis of major depressive disorder (n=198) resulted in a modest attenuation of the effect estimates in persons with depressive symptoms only, but did not materially change the effect estimates or significance levels in the apathy groups (data not shown).

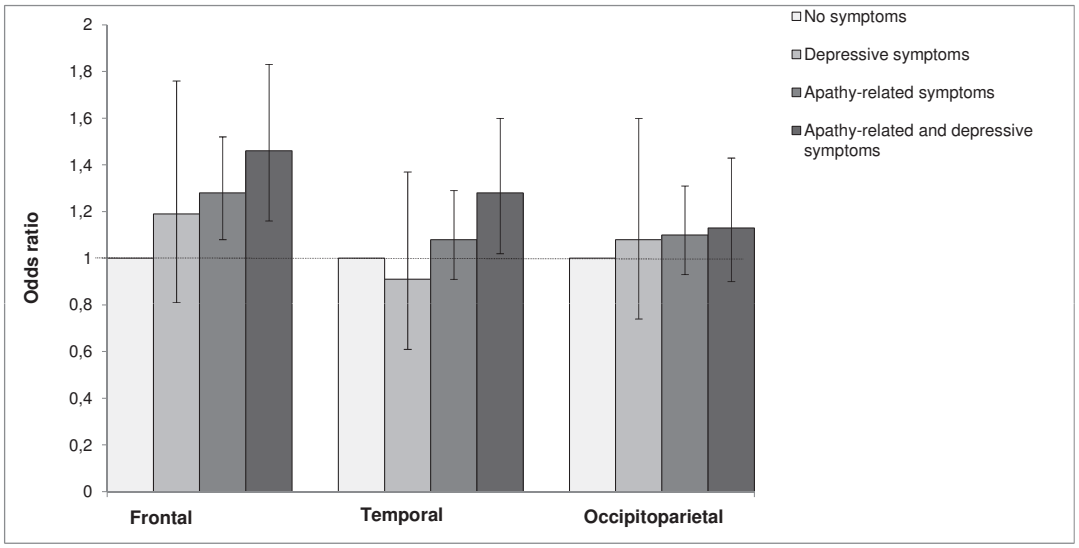

Figure 2 Odds ratios of the presence of cortical and subcortical infarcts for categories of apathy-related and depressive symptoms (with no apathy-related and no depressive symptoms as reference category), adjusted for age, sex, education and intracranial volume. Error bars indicate 95% confidence intervals.

Discussion

In this large scale population-based cohort study of non-demented older persons the four major findings were that 1) apathy-related symptoms are highly prevalent in the general older population, and remain unrecognized in the majority of persons when a traditional depression screening threshold such as a GDS-15 score ≥6 is used; 2) compared to those with no apathy-related and depressive symptoms, more brain atrophy, more WML and more infarcts were found only in persons with apathy-related symptoms, either alone or in combination with depressive symptoms; 3) apathy-related symptoms were not only associated with greater WML load in frontal regions, but also with more global and widespread gray matter atrophy and to a lesser extent also white matter atrophy; 4) relations between apathy-related symptoms and brain measures were independent of a lifetime history of major depressive disorder.

Important strengths of our study include the population-based design, the large sample size, the standardized assessment and exclusion of dementia and major depressive disorder, the

volumetric measurements of regional gray and white matter and WML, and the extensive assessment of vascular and behavioural factors for which we could adjust in our analyses.

A limitation is the cross-sectional design, which prevented us from examining whether brain atrophy and lesions precede apathy-related symptoms or whether both may result from a mutual underlying mechanism. In addition, we had no formal diagnosis of apathy and can thus only speak of apathy-related symptoms. However, various population-based studies have shown that the GDS-15 items used to define apathy symptoms in our study are indeed representative of apathy or withdrawal [31-33], and have therefore also been used as a measure of apathy in other studies [30, 34].

In our cohort, ≥2 apathy-related and no depressive symptoms were present in 35% of participants, and a combination of apathy-related and depressive symptoms was found in 14% of participants. Our findings are in line with other studies in the general older population that also found apathy-related symptoms to be among the most commonly reported symptoms in the GDS-15 questionnaire, ranging from 32% to 59% [32,41]. An important finding was that the majority of persons with two or more apathy-related symptoms scored below the traditional screening threshold on the GDS-15, indicating that these persons would not have been further screened for depression or other behavioural conditions. Moreover, our finding that 58% of participants preferred to stay at home suggests that these persons may be less likely to go out and seek help, which may contribute to an underdetection of apathy-related symptoms in clinical practice.

Various studies in patients with Alzheimer's disease found apathy to be associated with WML in the frontal region [19,20,42] and also with gray matter atrophy in medial frontal regions [21,22], striatum and thalamus [23]. Because gray matter atrophy in these regions is strongly related to cognitive performance [24], findings in demented persons may not altogether be generalized to the general older population. So far, we know of only one other study that investigated the relation between structural brain changes and apathy in a non-demented population-based sample. This study reported a relation between greater severity of deep WML and apathy [43]. Two other studies that assessed motivational symptoms found these to be associated with deep WML [44,45].

To our knowledge this is the first study in elders without dementia to investigate associations of apathy-related and depressive symptoms with different regional brain volumes. We found that in particular gait speed and vascular risk factors explained part of the relation between apathy-related symptoms and brain volumes, but brain volumes remained significantly smaller after adjustment for covariates. Our finding that apathy-related symptoms

were predominantly associated with atrophy and lesions of the frontal region, striatum, hippocampus/amygdala, and thalamus greatly resembles previous findings in patients with Alzheimer's disease. Associations of apathy with lesions in similar brain regions have also been reported in patients recovering from stroke [18]. An interesting finding was that the combined effect of apathy-related and depressive symptoms on frontal white-matter, striatum, hippocampus/amygdala, and thalamus volume was significantly greater than their additive effect. We do not have a clear explanation for this finding, and more studies are needed to replicate this finding.

Our study however also adds to the current literature in showing that gray matter atrophy and lesions associated with apathy are already present in older community-dwelling persons without dementia and independent of a history of stroke. These findings suggest that apathy may be a very early symptom of dementia, and that apathy symptoms are thus an early manifestation of cognitive decline. This hypothesis is supported by previous studies that identified apathy as one of the first neuropsychiatric symptoms in patients with MCI and dementia [46], but also as an independent risk factor for progression to dementia in patients with subjective memory problems and MCI [47-49]. Prospective studies are however needed to confirm this hypothesis.

When we examined regional WML load, we observed that apathy-related symptoms were primarily associated with the localization of greater WML load in the frontal region. This localization is in line with the concept of disruption of frontal-subcortical pathways as an underlying mechanism of late-life depressive symptoms, and could thus be interpreted as support for the 'vascular depression' hypothesis. Nevertheless, an important finding was that the relation between apathy symptoms and frontal WML load was independent of a lifetime diagnosis of major depressive disorder. On the one hand, this finding suggests that WML in frontal-subcortical pathways may be related to 'vascular apathy' rather than 'vascular depression' [50,51]. On the other hand, this finding also has important therapeutic consequences. Whereas serotonergic drugs are frequently prescribed and may be effective to relieve depression, these can cause or aggravate symptoms of apathy. Contrary, dopaminergic agents may relieve apathy but are ineffective as antidepressant [15]. In our cohort 10-15% of participants with apathy-related symptoms used SSRI's. Because we do not have information on the prescription indication, we can not distinguish whether SSRI use may have aggravated apathy symptoms in these persons, or whether serotonergic drugs may sometimes be prescribed to persons with apathy in whom other drug classes such as dopaminergic agents are more appropriate.

To conclude, apathy-related symptoms are common in community-dwelling older persons without dementia and often remain unrecognized when a traditional depression screening threshold is used. They are associated with an increased WML load in the frontal region, but also with a more diffuse and widespread loss of gray matter volume. These findings suggest that not only vascular pathology contributes to apathy, but also neurodegeneration.

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Supplementary table 1 Presence of underlying apathy-related and depressive symptoms in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study (n=4354)

	Total sample (n=4354)
Apathy-related symptoms, score ≥2 (%):	2108 (48)
- Dropped many activities or interests	1635 (38)
- Prefer to stay home	2528 (58)
- Not feeling full of energy	2194 (50)
Depressive symptoms, score ≥2 (%):	794 (18)
- Unsatisfied with life	233 (5)
- Feeling that life is empty	491 (11)
- Often feeling bored	304 (7)
- Not in good spirit most of the time	202 (5)
- Afraid something bad will happen	189 (4)
- Unhappy most of the time	192 (4)
- Often feeling helpless	436 (10)
- More memory problems	656 (15)
- Not wonderful to be alive	328 (8)
- Feeling pretty worthless	417 (10)
- Feeling that situation is hopeless	88 (2)
- Feeling that others are better off	53 (1)

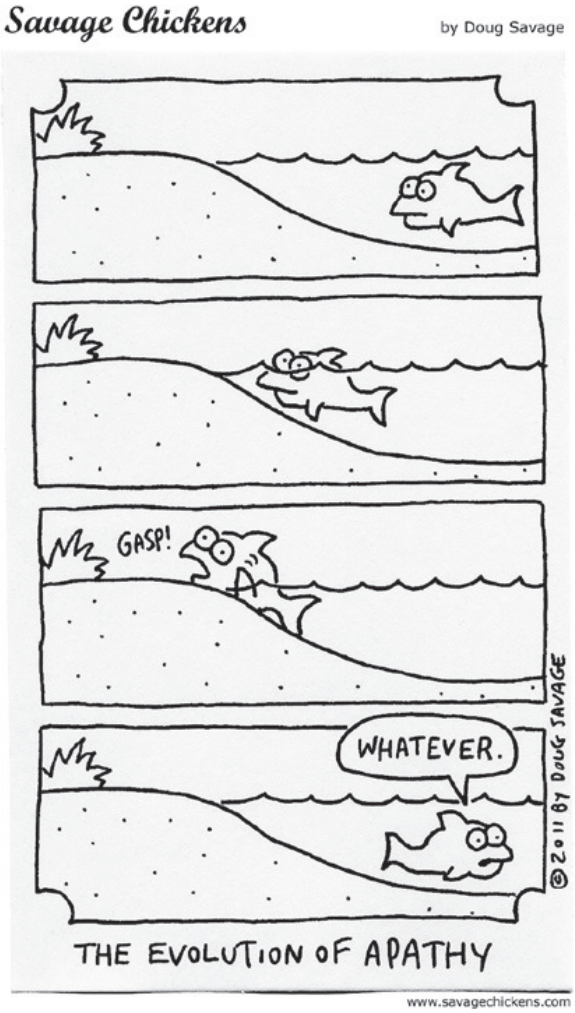
Supplementary table 2 Associations of apathy-related and depressive symptoms as independent, and infarcts in different brain regions as dependent variables (n=4354)

	Overall (n=4354)	No symptoms (n=2055)*	Depressive symptoms (n=191)	Apathy-related symptoms (n=1505)	Apathy-related and depressive symptoms (n=603)
	%	Ref	OR (95% CI)	OR (95% CI)	OR (95% CI)
Frontal:					
- Cortical	254 (6)	1.00	1.23 (0.60-2.50)	1.59 (1.17-2.14)	1.50 (1.01-2.26)
- Subcortical	358 (8)	1.00	0.69 (0.34-1.38)	1.06 (0.82-1.37)	1.35 (0.97-1.88)
Temporal:					
- Cortical	103 (2)	1.00	0.28 (0.04-2.04)	1.21 (0.76-1.91)	1.58 (0.89-2.82)
- Subcortical	279 (6)	1.00	0.93 (0.48-2.82)	1.21 (0.92-1.59)	1.13 (0.76-1.68)
Occipitoparietal					
- Cortical	271 (6)	1.00	0.71 (0.30-1.65)	1.45 (1.08-1.94)	1.49 (1.02-2.21)
- Subcortical	148 (3)	1.00	1.17 (0.49-2.74)	1.18 (0.81-1.72)	0.96 (0.55-1.65)
Striatum	448 (10)	1.00	0.83 (0.47-1.47)	1.13 (0.90-1.42)	1.28 (0.94-1.74)
Thalamus	58 (1)	1.00	0.67 (0.09-5.12)	1.85 (0.99-3.46)	1.42 (0.61-3.32)

* Reference category; Adjusted for age, sex, education, intracranial volume, smoking, alcohol use, body mass index, hypertension, diabetes mellitus, gait speed, coronary artery disease and antidepressant use

Chapter 7

General discussion



General discussion

In this thesis we investigated the influence of cerebral small-vessel disease and atrophy on self-rated functioning, depressive symptoms, cognitive performance and mortality; whether specific depression and cognition characteristics were related to strategic location of cerebral small-vessel disease in different brain regions; and the possible direction of causation between cerebral small-vessel disease, functioning and depressive symptoms.

Cerebral small-vessel disease and clinical presentation

Although cerebral small-vessel disease, characterized by white matter lesions (WML) and lacunar infarcts, is an often asymptomatic finding on brain magnetic resonance imaging (MRI) [1,2], it has been associated with an increased risk of physical and cognitive decline [3-5], late-life depression [6,7], future cardiovascular events and mortality [8]. In chapter 2.1 we found that progression of WML volume was also associated with a decline in more subjective measures of self-rated mental functioning. This finding is clinically relevant because lower self-rated mental and physical functioning are not only important outcome measures on an individual patient level, but also independent risk factors for cardiovascular events and mortality [9,10] (chapter 2.2). Moreover, in chapter 2.3 we found that the combined effect of lacunar infarcts and lower self-rated mental functioning on the risk of mortality exceeds their additive effects.

Increasing evidence supports a causal relationship between cerebral small-vessel disease and impairments in physical, mental and cognitive functioning. Several studies have shown that objective impairments in mental, physical and cognitive functioning are strongly related to the presence of cerebral small-vessel disease in strategic brain regions involved in the regulation of these different functions [11-15]. In chapter 4.1 we indeed found that associations of subcortical infarcts with depressive symptoms, executive functioning and memory depended on infarct location in deep white matter tracts and not on size. These findings provide support for the hypothesis that depression and physical or cognitive impairments may be direct manifestations of dysfunction of cerebral networks in these brain regions caused by cerebral small-vessel disease.

In recent years, the 'vascular depression' hypothesis in particular has drawn attention to the importance of lesion location in relation to late-life depression [16,17]. According to the 'vascular depression' hypothesis, disruption of prefrontal structures or connecting subcortical pathways by cerebral small-vessel disease may predispose, precipitate or perpetuate late-life depression [16]. Although some literature has supported the concept of 'vascular depression' [14,18,19], it has been increasingly questioned whether the behavioural problems associated with disruption of frontal-subcortical circuits by cerebral small-vessel

disease should be truly considered as characteristics of (vascular) depression. Instead, these motivational symptoms may be seen as manifestations of a behavioural syndrome in a much broader sense. In addition, it is unclear whether cerebral small-vessel disease may actually be a cause or a consequence of late-life depression. Although most studies identified cerebral small-vessel disease as a risk factor for physical and cognitive decline, the direction of causation seems less clear for late-life depression. Therefore, we will now discuss the controversies in the literature on 'vascular depression' and how the findings described in this thesis may contribute to a better understanding of the influence of cerebral small-vessel disease on behavioural problems.

The 'vascular depression' hypothesis

The 'vascular depression' hypothesis [16,17] proposed disruption of frontal-subcortical circuits, leading to impaired nerve conduction in brain regions involved in the regulation of emotions, as a mechanism by which cerebral small-vessel disease predisposes to late-life depression. Therefore, symptoms associated with dysregulation of behavioural and emotional functions in these brain regions have been considered as characteristic features of 'vascular depression' [15]. These symptoms are primarily characterized by the presence of motivational problems, including diminished interest and energy, psychomotor retardation and poorer executive functioning [11].

In support of the 'vascular depression' hypothesis, various cross-sectional studies observed a relationship between more severe WML and presence of clinically relevant depressive symptoms [20,21], which mainly depended on deep WML [14]. Nevertheless, contradictory results have also been reported, suggesting either a relation between depressive symptoms and lacunar infarcts but not WML [22,23], or no significant relationship at all [24]. Moreover, since longitudinal studies yielded highly inconsistent findings [21,25-28], it remains uncertain whether WML and lacunar infarcts are causally related to depression, or whether both may result from a mutual underlying mechanism.

The inconsistencies in findings from longitudinal studies may be explained in different ways. First, in chapter 5.2 we demonstrated that the presence of lacunar infarcts in deep white-matter was associated with more severe depressive symptoms during three years follow-up. The severity of depressive symptoms in these patients was not constant but showed a pattern of repeated exacerbations over time. Considering the fluctuations in depressive symptom severity over time in patients with lacunar infarcts, the strength of the relationship between lacunar infarcts or WML and depressive symptoms may therefore strongly depend on the time of depression assessment.

An alternative explanation could be that the relationship between cerebral small-vessel disease and depressive symptoms may in fact be bidirectional. So far, one study found that depression, defined as lifetime major depressive episode or current antidepressant use, may be a risk factor for the progression of WML volume [25]. These findings should however be interpreted with caution, since we showed in chapter 3.1 that this relation may be explained by antidepressant use rather than by symptoms of depression.

Third, most studies investigating the relation between cerebral small-vessel disease and depression used a cut-off score to define clinically relevant depressive symptoms, rather than to identify underlying symptom characteristics. In chapters 5.1 and 6.1 we demonstrated that the presence of WML and lacunar infarcts in deep white-matter and basal ganglia is particularly related to more severe motivational symptoms, but that in the majority of participants the overall symptom severity falls below standard thresholds used to define clinically relevant depressive symptoms and therefore may remain unrecognized when a standard cut-off score is used.

Motivational symptoms have been proposed as dominant features of 'vascular depression'[16,29]. Although one study confirmed cerebral small-vessel disease to be related to more motivational symptoms in older depressed individuals [19], recent findings suggested that a similar association may be found in persons without a depression diagnosis [30]. In chapter 5.1 we indeed demonstrated that WML and lacunar infarcts in deep white-matter tracts were associated with more severe motivational symptoms also in the absence of major depressive disorder, suggesting that these symptoms may in fact be manifestations of a more general motivational syndrome rather than (vascular) depression characteristics. Considering the great resemblance in symptom characteristics between apathy and the motivational items of depression rating scales [31,32], it may well be that the motivational symptoms associated with cerebral small-vessel disease are manifestations of apathy rather than depression [33].

Distinction between apathy and depression

Apathy is defined as reduced goal-directed activity in the behavioural, cognitive and emotional domains [34] and is characterized by diminished initiation, blunted emotional response, low social engagement, indifference and poor persistence, psychomotor retardation and energy problems [35,36]. Despite the overlap in symptom characteristics, apathy is essentially different from depression with regard to risk factors, clinical prognosis and pharmacological treatment [37]. Another important difference between apathy and depression is that symptoms of depressed mood, guilt, suicidal thoughts and feelings of hopelessness and worthlessness are absent in apathy [38].

In patients with stroke, mild cognitive impairment and Alzheimer's disease, apathy is one of the earliest and most common neuropsychiatric symptoms [39,40]. In these patients, the presence of apathy has been associated with more severe WML and lacunar infarcts in the frontal lobe and basal ganglia as well as with atrophy of the frontal gray matter, striatum and thalamus [40]. Because these changes are commonly present on brain MRI in patients with mild cognitive impairment and Alzheimer's disease and strongly related to cognitive performance [41], it is however unclear whether these findings can be altogether generalized to non-demented older persons. In chapter 6.1 we demonstrated that in non-demented older persons structural brain changes and apathy may be related in two different ways. First, we found cerebral small-vessel lesions and atrophy in frontal regions, basal ganglia and thalamus to be associated with presence of apathy-related symptoms, providing support for the concept of disruption of frontal-subcortical pathways. An important finding was that the observed associations were independent of major depressive disorder, suggesting that disruption of frontal-subcortical pathways may indeed predispose to apathy rather than (vascular) depression. On the other hand, we observed that apathy-related symptoms were associated with more global gray and white matter atrophy in all brain regions, suggesting that apathy-related symptoms may also occur as an early manifestation of cognitive decline.

The distinction between apathy and depression is clinically relevant on the level of the general health system, but also on an individual level. First, major depression is relatively rare (1.8%) in late-life [42], and forms a heterogeneous disorder that has been linked to different etiological pathways [43]. The 'vascular depression' hypothesis refers to a proportion of patients with late-life depression in whom cerebral small-vessel disease may predispose to a characteristic motivational presentation of depression (figure 1a). The distinction with apathy is important, because apathy is much more common in late-life than depression [44] and is associated with substantial caregiver distress, functional and cognitive decline and worse treatment response contributing to chronicity of symptoms [40]. As shown in chapter 6.1, the influence of cerebral small-vessel disease will be severely underestimated when we only focus on those with (vascular) depression, because the majority of patients with apathy-related symptoms do not fulfil the criteria for clinically relevant depressive symptoms or late-life depression (figure 1b).

Second, the 'vascular depression' hypothesis has focussed primarily on the relation between cerebral small-vessel disease and late-life depression. Various studies however observed that besides cerebral small-vessel disease, brain atrophy may also be independently associated with depressive symptoms [21,45]. In chapter 6.1 we observed that the presence of clinically relevant depressive symptoms was associated not only with cerebral small-vessel disease but also with more gray and white matter atrophy.

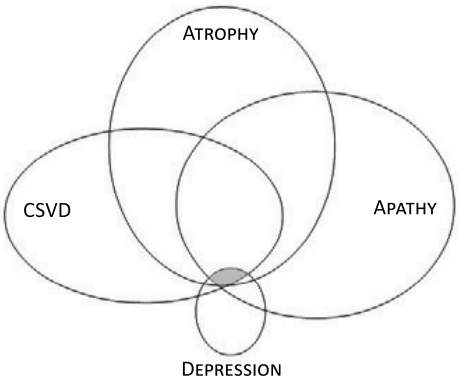


Figure 1a

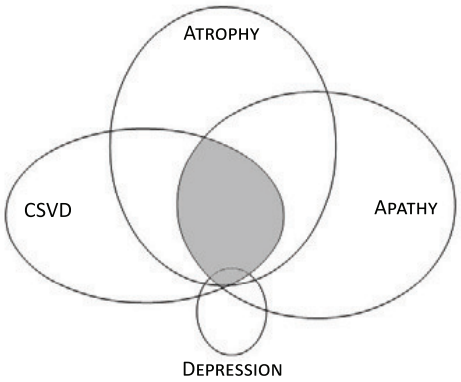


Figure 1b

These associations were primarily driven by apathy-related symptoms and not by symptoms of depressed mood. These findings suggest that the actual number of persons in whom apathy symptoms may be related to structural brain changes is much larger than in those with cerebral small-vessel disease alone (figure 1c).

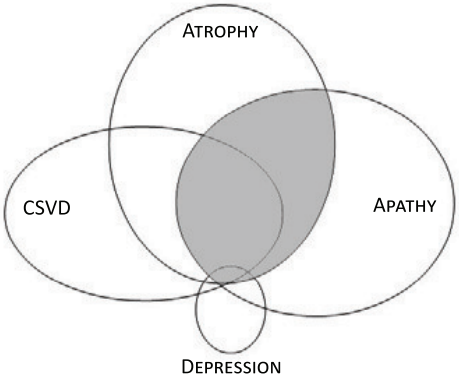


Figure 1c

Third, distinguishing apathy from depression has important therapeutic consequences. Whereas serotonergic drugs can relieve depression, these may increase the severity of apathy [46]. Dopaminergic agents on the other hand may relieve apathy symptoms, but are ineffective as antidepressant medication.

Conclusions and future directions

The postulation of the 'vascular depression' hypothesis has inspired many researchers to investigate disruption of prefrontal and subcortical circuits by cerebral small-vessel disease as an underlying mechanism of late-life depression. This concept seems attractive because

other risk factors for late-life depression remain unclear or may be difficult to manipulate [40,47]. Several studies on the other hand suggested that progression of WML and lacunar infarcts may be delayed through strict regulation of cardiovascular risk factors, such as intensive treatment of hypertension [48], statin use [49,50] and the application of a multicomponent vascular care program [51]. Future studies are however needed to investigate whether these vascular intervention programs may actually lead to prevention or amelioration of motivational symptoms.

To conclude, different studies provided support for the concept of frontal-subcortical dysfunction as a mechanism by which structural brain changes are associated with motivational symptoms in later life. It is however important to realise that the relation between structural brain changes and motivational symptoms is not inextricably linked to depression but may also be explained by apathy. If we focus on apathy-related symptoms a much larger proportion of older persons at risk of a poor clinical prognosis may be identified. This may prove more useful than assessment of depression or clinically relevant depressive symptoms. It may be time to give a voice to those left behind and translate the concept of 'vascular depression' to a much broader population of older persons (figure 2).

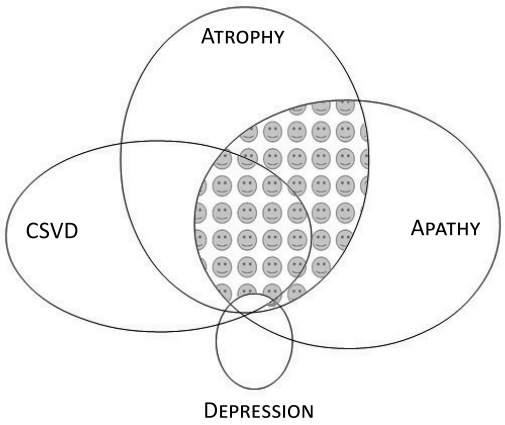


Figure 2

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Chapter 8

Summary

Nederlandse samenvatting

Dankwoord

Curriculum Vitae

Summary

Cardiovascular disease is a common and important health problem, with ischemic heart disease and stroke as top contributors to morbidity and mortality worldwide. During the lifespan, cardiovascular disease is associated with substantial impairments in self-rated health status and an increased risk of late-life depression and cognitive decline. Despite the large number of candidate mechanisms that have been investigated, the exact underlying mechanisms explaining the relation between cardiovascular disease and depression, cognitive impairment and poorer self-rated functioning remain unknown. One of the potential mechanisms is the presence of vascular disease-related structural brain changes, characterized by white matter lesions (WML), lacunar infarcts and atrophy on magnetic resonance imaging (MRI).

The 'vascular depression' hypothesis proposed that disruption of frontal-subcortical networks resulting in impaired neural connectivity may be a mechanism by which WML and lacunar infarcts predispose, precipitate or perpetuate depression in late life. In this thesis we investigated the influence of cerebral small-vessel disease and atrophy on self-rated health status, cognitive performance, depressive symptoms and mortality; whether different depressive symptom characteristics and impairments in cognitive functioning are related to the strategic location of WML, lacunar infarcts and atrophy in distinct brain regions; and the possible direction of causation between WML and lacunar infarcts, self-rated functioning and depressive symptoms.

Cerebral small-vessel disease, self-rated health status and clinical prognosis

We first investigated the influence of increased progression of WML volume on changes in self-rated physical and mental health status during four years follow-up in patients with symptomatic atherosclerotic disease (486 participants, 58±9 years; 80% male) (**chapter 2.1**). We found that overall physical health status increased, whereas mental health status decreased in survivors of a symptomatic atherosclerotic event. A more pronounced progression of WML volume contributed to an even stronger decline in mental health status, but did not influence changes in physical health status.

Poorer self-rated physical and mental health status are not only associated with a lower subjective well-being, but are also thought to be relevant for the clinical prognosis of patients with cardiovascular disease. In **chapter 2.2** we investigated whether poorer self-rated health status was associated with a worse clinical prognosis in patients with different manifestations of symptomatic and asymptomatic atherosclerotic disease (5877 participants, 56±12 years; 67% male) during four years follow-up. We found that lower self-rated physical and mental health status were both independent risk factors for future vascular events

and mortality; and that these risks did not differ between patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, and asymptomatic atherosclerotic disease.

Although a relation between depression and mortality has been frequently observed, the underlying pathophysiological mechanisms remain largely unknown. In **chapter 2.3** we investigated the influence of WML and lacunar infarcts on the relation between mood problems and mortality in patients with symptomatic atherosclerotic disease (1110 participants, 59±10 years; 78% male) during six years follow-up. We found that the combined effect of lacunar infarcts and mood problems on the risk of mortality exceeded their additive effects, suggesting that patients with lacunar infarcts are particularly vulnerable to the effect of mood problems on poor outcome.

Antidepressant use and cerebral small-vessel disease

Various studies found a cross-sectional relation between WML and depressive symptoms. Because WML and depressive symptoms were measured at the same moment in time, the direction of causation remains unclear. In **chapter 3.1** we investigated whether depressed mood at baseline, defined as mood problems and/or antidepressant use, was related to an increased severity and progression of WML volume during four years follow-up (594 participants, 58±10 years; 80% male). We found that depressed mood at baseline was not associated with a greater baseline volume or an increase in WML volume during follow-up. However, when separate contributions were distinguished, antidepressant use was associated with greater WML volume at baseline and a modest, although not statistically significant increase in WML volume during follow-up, while mood problems were not.

Location of cerebrovascular disease, depression and cognition

Depression and cognitive impairment are common and disabling disorders in later life, and moreover frequently co-occur. Structural cerebral changes, including atrophy and cerebrovascular changes, may contribute to depression as well as to cognitive impairment in later life. In **chapter 4.1** we investigated the influence of atrophy, WML and infarcts in different brain regions on the risk of depressive symptoms and cognitive functioning in patients with symptomatic atherosclerotic disease without dementia (585 participants, 63±8 years; 82% male). We found that subcortical infarcts were associated with depressive symptoms as well as poorer executive functioning and memory. These associations depended on location in deep white matter tracts rather than on infarct size. Periventricular WML, cortical infarcts and atrophy on the other hand were associated with poorer executive functioning and slowed processing speed, but not with depressive symptoms.

Another study investigated the influence of deep and periventricular WML volume on depression by comparing WML volumes in 22 patients with late-onset major depression and 22 healthy controls. The authors found a relation between deep WML localization and late-onset depression, whereas no associations of the number and the volume of deep WML with late-onset depression were found. These findings may be of significance, however some considerations need to be taken into account during the interpretation, as discussed in **chapter 4.2**.

Location of cerebral small-vessel disease and depressive symptom profiles

Because motivational problems are considered as dominant features of frontal-subcortical dysfunction, these symptoms have been suggested as characteristic features of 'vascular depression'. Few studies have directly investigated the relationship between cerebral-small vessel and degenerative changes on MRI and underlying depressive symptom characteristics. In **chapter 5.1** we investigated the influence of location and progression of lacunar infarcts, WML and atrophy on the risk of motivational and mood symptoms in patients with symptomatic atherosclerotic disease (578 participants, 63±8 years; 83% male). In line with the concept of frontal-subcortical dysfunction, we found that lacunar infarcts and WML in deep white matter tracts were primarily associated with the presence of motivational problems, while atrophy was associated with a more mixed symptom profile. The finding that greater progression of WML volume was associated with an increased risk of primarily motivational symptoms, suggests that WML volume may contribute to or precede motivational problems. Interestingly, observed associations were independent of major depressive disorder.

In addition, we examined the influence of lacunar infarcts and WML volume on the course of depressive symptoms during three years follow-up in patients with symptomatic atherosclerotic disease in **chapter 5.2** (650 participants, 62±9 years; 81% male). We observed that the presence of lacunar infarcts in deep white matter tracts was associated with a more severe and fluctuating course of depressive symptoms, and that these symptoms were primarily characterized by motivational problems. Excluding patients with major depressive disorder at baseline did not change this association, suggesting that these problems may be expressions of apathy or a motivational syndrome in a much broader sense rather than 'vascular depression' characteristics.

Brain volume, cerebral small-vessel disease and apathy

In dementia, apathy commonly occurs and is associated with structural brain abnormalities. Although apathy is also common in non-demented persons, its association with brain changes is unclear. In **chapter 6.1** we investigated whether apathy-related symptoms were

associated with brain volumes, white matter lesions (WML) and infarcts in a population-based cohort of older persons without dementia (4354 participants, 76±5 years; 41% male). Compared to participants without symptoms, persons with only apathy-related symptoms had smaller gray matter volumes in all lobes and an increased WML load in the frontal lobe. Persons with a combination of apathy-related and depressive symptoms had significantly smaller gray as well as white matter volumes in all lobes, smaller striatum, hippocampus complex and thalamus volumes, and an increased frontal WML load. Excluding participants with major depressive disorder did not change these associations.

In **chapter 7** we discussed the findings of this thesis within the framework of the 'vascular depression' hypothesis. First, the findings of this thesis suggest that cerebral small-vessel disease is associated with the presence of depressive symptoms, and that this relation not only depends on lesion severity but also on the location in frontal and deep white matter tracts. Second, these symptoms are characterized by the presence of motivational rather than mood problems. In so far, our results are in line with the 'vascular depression' hypothesis. However, we found that the observed relation between cerebral small-vessel disease and motivational problems did not depend on the presence of major depressive disorder in either the SMART cohort or the AGES-Reykjavik cohort. These findings suggest that cerebral small-vessel disease may in fact be associated with 'vascular apathy' rather than 'vascular depression'.

Future studies are needed to investigate whether the findings in this thesis can be generalized to the general population. In addition, repeated follow-up measurements are necessary to investigate whether cerebral small-vessel may truly be a cause of motivational problems, a consequence, or whether both may result from a mutual underlying mechanism. Finally, we found that not only vascular pathology contributes to apathy, but also neurodegeneration. To investigate whether apathy may be an early manifestation of cognitive decline, longitudinal studies are needed to examine whether persons with apathy are at increased risk of dementia.

Chapter 8

Nederlandse samenvatting

Hart- en vaatziekten vormen een veelvoorkomend en belangrijk gezondheidsprobleem. Wereldwijd behoren ischemische hartziekte en beroerte tot de voornaamste veroorzakers van een verhoogde morbiditeit en sterfte. Patiënten met hart- en vaatziekten ervaren veelal substantiële beperkingen in hun gezondheid, en lopen bovendien een verhoogd risico op zowel depressie als cognitieve achteruitgang. Tot op heden is het exacte onderliggende mechanisme dat de relatie tussen hart- en vaatziekten, depressie, cognitieve achteruitgang en zelf-gerapporteerd slechter functioneren kan verklaren nog onbekend. Eén van de potentiële mechanismen is de aanwezigheid van vasculair gerelateerde structurele breinveranderingen, die gekenmerkt wordt door de aanwezigheid van witte stof lesies, lacunaire infarcten en atrofie op MRI.

De 'vasculaire depressie' hypothese stelt dat de onderbreking van frontaal-subcorticale hersenbanen, resulterend in een verstoorde zenuwgeleiding, een mechanisme kan zijn waardoor witte stof lesies en lacunaire infarcten depressie op latere leeftijd kunnen veroorzaken of verergeren. In dit proefschrift hebben we de invloed van microvasculaire schade en atrofie in de hersenen op zelf-gerapporteerde gezondheid, cognitief functioneren, depressieve symptomen en sterfte onderzocht; of verschillende typen depressieve symptomen en beperkingen in cognitief functioneren gerelateerd zijn aan de specifieke lokatie van witte stof lesies, lacunaire infarcten en atrofie in verschillende hersengebieden; en de richting van het mogelijke verband tussen witte stof lesies en lacunaire infarcten, zelf-gerapporteerd functioneren en depressieve symptomen.

Microvasculaire hersenschade, zelf-gerapporteerde gezondheid en klinische prognose

Ten eerste hebben we de invloed onderzocht van een verhoogde progressie van witte stof lesies op de verandering in zelf-gerapporteerde fysieke en mentale gezondheid gedurende vier jaar follow-up bij patiënten met symptomatisch vaatlijden (486 deelnemers, 58±9 jaar; 80% man) (**hoofdstuk 2.1**). We vonden hierbij dat fysieke gezondheid gemiddeld gezien verbeterde, terwijl de mentale gezondheid afnam bij patiënten in de herstelfase van een vasculaire event. Een verhoogde progressie van witte stof lesies droeg bij aan een nog sterkere afname van de mentale gezondheid, terwijl deze geen invloed had op de verandering in fysieke gezondheid.

Een zelf-gerapporteerde slechtere fysieke en mentale gezondheid hangt niet alleen samen met een verminderd welbevinden van de patiënt, maar lijkt ook van belang te zijn voor het ziekteverloop van patiënten met hart- en vaatziekten. In **hoofdstuk 2.2** hebben we onderzocht of er een samenhang is tussen een zelf-gerapporteerde slechtere gezondheid en een verminderde ziekte prognose bij patiënten met verschillende uitingen van symptomatisch

en asymptomatisch vaatlijden (5877 deelnemers, 56±12 jaar; 67% man) gedurende vier jaar follow-up. Hierbij hebben we gevonden dat zowel een zelf-gerapporteerde slechtere fysieke als ook mentale gezondheid een onafhankelijke risicofactor is voor nieuwe vasculaire complicaties en sterfte; en dat dit risico niet verschilt tussen patiënten met coronairlijden, cerebraal vaatlijden, perifeer vaatlijden, aneurysma aorta abdominale en asymptomatisch vaatlijden.

Alhoewel in verschillende studies een relatie is gevonden tussen depressie en een verhoogde sterfte, is het onderliggende pathofysiologische mechanisme vooralsnog onbekend.
In **hoofdstuk 2.3** hebben we de invloed van witte stof lesies en lacunaire infarcten op de relatie tussen stemmingsproblemen en sterfte onderzocht bij patiënten met symptomatisch vaatlijden (1110 deelnemers, 59±10 jaar; 78% man) gedurende zes jaar follow-up. Hierbij vonden we dat het gecombineerde effect van lacunaire infarcten en stemmingsproblemen op het risico op overlijden veel sterker was dan de optelsom van beide effecten, wat suggereert dat patiënten met lacunaire infarcten extra gevoelig zijn voor het effect van stemmingsproblemen op overlijden.

Antidepressiva gebruik en microvasculaire hersenschade
Verschillende studies hebben een cross-sectioneel verband aangetoond tussen witte stof lesies en depressieve symptomen. Omdat zowel witte stof lesies als depressieve symptomen op hetzelfde moment in de tijd zijn gemeten, is de richting van het verband echter onduidelijk. In **hoofdstuk 3.1** hebben we onderzocht of een depressieve stemming op baseline, gedefinieerd als de aanwezigheid van stemmingsproblemen en/of antidepressivagebruik, gerelateerd was aan een verhoogde ernst en progressie van witte stof lesie volume gedurende vier jaar follow-up (594 deelnemers, 58±10 jaar; 80% man). Hierbij hebben we gevonden dat een depressieve stemming op baseline niet geassocieerd was met een verhoogde ernst of progressie van witte stof lesie volume gedurende follow-up. Wanneer de individuele bijdrage van stemmingsproblemen en antidepressiva werd onderscheiden, was antidepressiva gebruik echter geassocieerd met een verhoogd witte stof lesie volume op baseline en met een bescheiden, alhoewel statistisch niet significante toename in de progressie van witte stof lesie volume tijdens follow-up, terwijl geen relatie met stemmingsproblemen werd gevonden.

Lokatie van cerebrovasculaire ziekte, depressie en cognitie
Depressie en cognitieve beperkingen zijn veelvoorkomende en belemmerende aandoeningen op latere leeftijd, die bovendien vaak tegelijkertijd optreden. Structurele veranderingen in de hersenen, zoals atrofie en cerebrovasculaire veranderingen, zouden kunnen bijdragen aan het ontstaan van zowel depressie als verminderd cognitief functioneren op latere

leeftijd. In **hoofdstuk 4.1** hebben we de invloed van atrofie, witte stof lesies en infarcten in verschillende hersengebieden op het risico op depressieve symptomen en cognitief functioneren onderzocht bij patiënten met symptomatisch vaatlijden zonder dementie (585 deelnemers, 63±8 jaar; 82% man). Hierbij hebben we gevonden dat subcorticale infarcten geassocieerd waren met zowel depressieve symptomen als verminderd executief functioneren en geheugen. Deze associaties berustten op de locatie van subcorticale infarcten in diepe witte stof banen en niet op de grootte van het infarct. Periventriculaire witte stof lesies, corticale infarcten en atrofie aan de andere kant waren geassocieerd met verminderd executief functioneren en een vertraagde verwerkingssnelheid, maar niet met depressieve symptomen.

In een ander onderzoek is de invloed onderzocht van diepe en periventriculaire witte stof lesies op depressie door het witte stof lesie volume te vergelijken van 22 patiënten met depressie op latere leeftijd en 22 gezonde controlepersonen. De auteurs vonden een relatie tussen de lokatie van lesies in de diepe witte stof en depressie op latere leeftijd, terwijl geen relatie werd gevonden met het aantal en het volume van diepe witte stof lesies. Alhoewel deze bevindingen van belang kunnen zijn, verdient het aanbeveling om een aantal factoren in ogenschouw te nemen die deze relaties mogelijk kunnen hebben beïnvloed, zoals besproken in **hoofdstuk 4.2**.

Lokatie van microvasculaire hersenschade en depressieve symptoomprofielen

Aangezien frontaal-subcorticale dysfunctie voornamelijk gekenmerkt wordt door motivationele problemen, worden deze symptomen beschouwd als karakteristieke kenmerken van 'vasculaire depressie'. Er zijn echter weinig studies die de directe relatie tussen microvasculaire schade en atrofie van de hersenen op MRI, en onderliggende kenmerken van depressieve symptomen hebben onderzocht. In **hoofdstuk 5.1** hebben we de invloed onderzocht van de lokatie en progressie van lacunaire infarcten, witte stof lesies en atrofie op het risico op motivationele en stemmingssymptomen bij patiënten met symptomatisch vaatlijden (578 deelnemers, 63±8 jaar; 83% man). In lijn met het concept van frontaal-subcorticale dysfunctie, hebben we gevonden dat lacunaire infarcten en witte stof lesies in diepe witte stof banen met name geassocieerd waren met de aanwezigheid van motivationele problemen, terwijl atrofie geassocieerd was met een gemengd symptoomprofiel. Daarnaast suggereert onze bevinding dat een verhoogde progressie van witte stof lesies geassocieerd was met een toegenomen risico op motivationele symptomen, dat witte stof lesies zouden kunnen voorafgaan of bijdragen aan het ontstaan van motivationele problemen. Een opmerkelijke bevinding was dat de geobserveerde relaties onafhankelijk waren van het wel of niet hebben van een depressie diagnose.

Daarnaast hebben we in **hoofdstuk 5.2** de invloed onderzocht van lacunaire infarcten en witte stof lesies op het verloop van depressieve symptomen gedurende drie jaar follow-up bij patiënten met symptomatisch vaatlijden (650 deelnemers, 62±9 jaar; 81% man). We hebben gevonden dat de aanwezigheid van lacunaire infarcten in diepe witte stof banen geassocieerd was met een ernstiger en fluctuerender verloop van depressieve symptomen, en dat deze symptomen met name gekenmerkt werden door motivationele problemen. Deze relatie veranderde niet wanneer patiënten met een depressie diagnose werden geëxcludeerd, wat suggereert dat deze symptomen wellicht eerder uitingen van apathie of een motivationeel syndroom in bredere zin zouden kunnen zijn dan kenmerken van 'vasculaire depressie'.

Breinvolume, microvasculaire hersenschade en apathie

Bij patiënten met dementie is apathie een veelvoorkomende aandoening die geassocieerd is met de aanwezigheid van structurele breinveranderingen. Alhoewel apathie ook vaak voorkomt bij ouderen zonder dementie, is de relatie met breinveranderingen bij deze personen onduidelijk. In **hoofdstuk 6.1** hebben we onderzocht of apathie-gerelateerde symptomen geassocieerd zijn met breinvolume, witte stof lesies en infarcten bij oudere personen zonder dementie (4354 deelnemers, 76±5 jaar; 41% man). In vergelijking met deelnemers zonder symptomen, hadden personen met enkel apathie-gerelateerde symptomen lagere grijze stof volumes in alle hersenkwabben en meer witte stof lesies in de frontaalkwab. Personen met zowel apathie-gerelateerde als depressieve symptomen hadden lagere grijze en witte stof volumes in alle hersenkwabben, lagere volumes van het striatum, hippocampuscomplex en thalamus, en meer witte stof lesies in de frontaalkwab. Deze associaties veranderden niet wanneer personen met een depressie werden geëxcludeerd.

In **hoofdstuk 7** hebben we vergeleken in hoeverre de bevindingen in dit proefschrift overeenkomen met het concept van de 'vasculaire depressie' hypothese. Onze bevindingen suggereren ten eerste dat microvasculaire schade in de hersenen geassocieerd is met de aanwezigheid van depressieve symptomen, en dat deze relatie niet alleen berust op de ernst van de afwijkingen maar ook op de lokatie in frontale en diepe witte stof banen. Daarnaast hebben we gevonden dat deze depressieve symptomen gekenmerkt worden door de aanwezigheid van motivationele problemen en niet door stemmingsproblemen. In zoverre komen onze bevindingen overeen met de 'vasculaire depressie' hypothese. Echter, zowel in de SMART studie als in het AGES-Reykjavik cohort hebben we gevonden dat de relatie tussen microvasculaire schade in de hersenen en motivationele problemen niet afhing van de aanwezigheid van een depressie diagnose. Dit suggereert dat microvasculaire schade in de hersenen eerder geassocieerd is met 'vasculaire apathie' dan met 'vasculaire depressie'.

Toekomstige studies zullen moeten aantonen of de bevindingen in dit proefschrift gegeneraliseerd kunnen worden naar de algemene bevolking. Daarnaast zijn herhaalde follow-up metingen noodzakelijk om te onderzoeken of microvasculaire schade aan de hersenen daadwerkelijk een oorzaak is van motivationele problemen, een gevolg, of dat beiden veroorzaakt worden door eenzelfde onderliggend mechanisme. Tenslotte hebben we gevonden dat niet alleen vasculaire pathologie, maar ook neurodegeneratie kan bijdragen aan apathie. Longitudinale studies die het risico op dementie onderzoeken bij personen met apathie, zijn nodig om te bepalen of apathie een vroege uiting zou kunnen zijn van cognitieve achteruitgang.

Curriculum Vitae

Anne Merlijn Grool was born on October 2, 1981 in Ede, the Netherlands. After graduating from secondary school 'Het Marnix College' in Ede in 2000, she studied Medicine at the University of Groningen. During the final year of her medical degree, she conducted six months of scientific research in Auckland, New Zealand, at the Audiology Clinic. After graduating in December 2006, she worked as a medical intern in the Intensive Care Unit at the Gelderse Vallei hospital in Ede. From May 2008 until December 2011, Anne worked on the research project 'Cerebral small-vessel disease and depression in patients with manifest arterial disease: cause or consequence?' at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht under the supervision of Prof.dr. Y. van der Graaf, Prof.dr. W.P.T.M. Mali and Dr. M.I. Geerlings. She obtained her degree in Clinical Epidemiology at Utrecht University in 2011. In January 2012 she began her medical residency in Radiology at the University Medical Center Utrecht, the Netherlands.