The weight of subclinical vascular disease & neuroticism in late-life depression
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Summary and general discussion
Introduction

The main aim of this thesis was to study the association between subclinical vascular disease and late-life depression, taking into account different depressive symptom clusters and the interplay with neuroticism. In part one we focused on the association between depression and metabolic syndrome as a major risk factor for vascular disease. In part two we focused on the association between depression and the severity of atherosclerosis as a direct marker of subclinical vascular disease. In this second part, we also examined the interplay between subclinical vascular disease and neuroticism as a second (and more traditional) risk factor for depression.

The studies described in this thesis were mainly conducted in population-based samples of middle-aged and older persons, i.e. the Nijmegen Biomedical Study (chapter 2, 3, 5 and 6) and the Longitudinal Aging Study Amsterdam (chapter 7), with the exception of one study in the Netherlands Study of Depression in Older persons (NESDO), including 378 older persons suffering from a depressive disorder according to DSM-IV-TR criteria (chapter 4). This thesis illustrates the complexities of late-life depression. First, allowing for different depressive symptom profiles, i.e. the actual phenotypic expression. Secondly, by examining the interplay between a major psychological risk factor, i.e. neuroticism, and biological risk factors, i.e. subclinical vascular disease. Finally, by pointing to discrepancies between population-based and clinical samples. The following paragraphs will summarise the findings in the different chapters of this thesis, leading to a general discussion in which overall conclusions will be made and methodological considerations will be identified. Finally, after going back to the consequences of this thesis for the case reports, further implications for clinical practice and recommendations for future studies will be described.

Depressive symptom profiles and the metabolic syndrome

Several studies have found an association between depression and the metabolic syndrome (Koponen et al, 2008; Akbaraly et al, 2011; Pan et al, 2012) as well as with obesity assessed by Body Mass Index (BMI) (de Wit et al, 2010; Luppino et al, 2010). In chapter 2 and 3 we extended these findings by examining specifically the association between depressive symptom profiles and the metabolic syndrome and different measures of obesity (not only BMI but also Waist Circumference and Waist-Hip-Ratio). These studies were conducted within a population based sample aged 50 through 70 years participating in the Nijmegen Biomedical Study (NBS).
In chapter 2 we showed that depressive symptoms (BDI sum score) are significantly associated with the presence of the metabolic syndrome and show even stronger associations with the number of metabolic risk factors. The association between metabolic syndrome and depressive symptoms was primarily driven by the somatic-affective symptom-cluster of depression. Exploring sex-differences, we found that in men waist circumference, triglycerides and HDL cholesterol explained the variance in depressive symptoms whereas in women this effect was confined to waist circumference. Although pathophysiological mechanisms underlying the association between metabolic disturbance and depression remains to be elucidated, future studies should take into account possible sex-differences as well as the specific phenotype of depression that is associated with metabolic disturbances.

**Depressive symptom profiles, late-life depressive disorder and obesity**

In chapter 3 we explored the association between obesity and depression in more depth. Meta-analyses have found a reciprocal association between body mass index (BMI) and depression (de Wit et al, 2010; Luppino et al, 2010). We found waist circumference as the central component of the metabolic syndrome in the association between the metabolic syndrome and depression. Previous studies on these associations, however, did not take into account different symptom profiles as well as different definitions of obesity. In line with earlier findings, we showed in chapter 3 the U-shaped relationship between Body Mass Index (BMI) and depressive symptoms. Excluding underweight patients, a positive correlation was found between BMI and all different measures of depressive symptoms e.g. BDI sumscore and the cognitive- and somatic-affective symptom clusters. These findings suggest that depressive symptoms in individuals with obesity may be affected by both psychological as well as physical pathways (Struijs et al, 2013). Measures of visceral obesity, however, were specifically associated with the somatic-affective symptom cluster (resp. waist circumference and Waist Hip Ratio). So visceral obesity, which is more indicative of vascular risk than BMI, is specifically associated with somatic-affective depressive symptoms. This finding might suggest that these symptoms are primarily due to a (subclinical) somatic condition. Although the differences between men and women were not statistically different, post hoc analyses showed larger effect sizes for women than for men in all depressive symptoms measures in relation to BMI and WC. Sex differences may also occur because women are more likely to be stigmatized for being overweight or obese than are men.
In chapter 4 we examined whether the association found in a population based sample could be replicated in a clinically depressed sample aged 60 years and over who participated in the Netherlands Study of Depression in Older persons (NESDO) (Comijs et al, 2011). We showed that depressed older patients had a significantly lower waist circumference compared to non-depressed controls. It is concluded that the population-based findings on the positive association between obesity and depressive symptoms cannot be generalised to patients suffering from a late-life depression. Multiple linear regression analyses within the depressed group showed that both depression severity (Inventory of Depressive Symptoms) and duration-related depression characteristics (age of onset, duration of illness, life-time comorbid dysthymia) were associated with the waist circumference. Only the severity of depressive symptoms remained significant after further adjustment for the body mass index. When looking specifically at symptom profiles, the motivation subscale became significant.

Visceral adipose tissue is metabolically active by secretion of cytokine-family proteins, collectively called adipokines (Trujillo and Scherer, 2006, Milanesi et al, 2012, Zhao and Stephens, 2013). These adipokines are hypothesized to induce a chronic low-grade inflammatory environment, thus contributing to the negative health effect of obesity. Some adipokines like leptin, resistin and adiponectin have been linked to mood regulation (Wilhelm et al, 2012; Milanesi et al, 2102). In chapter 2 we found that adiponectin neither mediated nor moderated any of the associations found between depressive symptoms, the metabolic syndrome or the individual components of the metabolic syndrome e.g. waist circumference. In chapter 4 we found that a recently discovered adipokine, Neutrophil Gelatinase-Associated Lipocalin (NGAL), was associated with late-life depression, but only in the subgroup of patients with a pathologically increased waist circumference. These findings indeed link the metabolic activity of visceral adiposity to depressive symptoms, but findings on adiponectin show that there may be specific associations (and function) of different adipokines.

**Depressive symptoms profiles, atherosclerosis and neuroticism**

The association of depressive symptoms with vascular disease has primarily been examined in studies looking at clinically manifest vascular disease like cardiac patients or stroke. As manifest vascular disease is the result of a life-long accumulation of vascular burden, we examined in chapter 5 whether depression and depressive symptom profiles were also associated with the severity of atherosclerosis. This study was also
conducted within a population based sample aged 50 through 70 years participating in the Nijmegen Biomedical Study (NBS). Generalized atherosclerotic disease can be reliably measured by the intima media thickness (IMT) of the carotid artery and has been associated consistently with a negative cardiovascular outcome (Bots et al, 1996, 1997). We found a significant association between the depressive symptoms (BDI sum-score) and subclinical atherosclerosis as measured by the Intima Media Thickness, both in patients with and without coronary artery disease. So the relationship seems to be specific for atherosclerotic disease independent of vascular events. Furthermore, the positive association between depressive symptoms and atherosclerosis is primarily driven by the somatic-affective symptom cluster of depression.

So, in middle-aged and older people in the general population, the association between depressive symptoms and subclinical atherosclerotic disease, visceral obesity and the metabolic syndrome could be explained by the somatic-affective symptom cluster within the depression symptomatology. This might suggest that these symptoms are primarily due to a (subclinical) somatic condition (Meijer et al, 2013). Subclinical vascular disease and the risk factors obesity and the metabolic syndrome in general might inflate depressive symptoms scores and may explain why treatment of depression in for example cardiac patients hardly effect vascular outcome (Glassman et al, 2002; Berkman et al, 2003; van Melle et al, 2007; Lespérance et al, 2007).

Subsequently, we were interested whether and how subclinical vascular disease would interact with another major risk factor for late-life depression, neuroticism, in explaining variance in these depressive symptom profiles. Based on two previous studies (Oldehinkel et al, 2003; Wouts et al, 2011), we expected that neuroticism and subclinical atherosclerotic disease as measured by Intima Media Thickness would negatively interact with regard to the presence of depressive symptoms. In chapter 6 we described that in our study neuroticism was associated with the total number of depressive symptoms and with both cognitive-affective and somatic-affective symptoms. The strength of this association was much larger than the association with subclinical as well as clinical vascular disease. Therefore, it is remarkably that neuroticism has been largely neglected in the field of late-life depression. We found a negative interaction between neuroticism and atherosclerosis in explaining variance of the cognitive-affective symptoms of depression, but not the somatic-affective symptoms. The effect of neuroticism in explaining depressive symptoms diminishes in the presence of more severe atherosclerosis. This may be explained by apathy due to cerebrovascular disease and fits the hypothesis of vascular apathy (see chapter 6).
Low neuroticism as a marker for subclinical vascular disease in late-life depression

Finally, based on previous findings in this thesis, we postulated in chapter 7 that the association between depression and vascular events is confounded by underlying vascular disease in later life and that this may differ for different subtypes of depression (vascular versus neurotic-associated depression). We expected that vascular depression, defined theoretically by a high aetiological contribution of vascular disease, increases the risk on future strokes, whereas neuroticism-associated depression does not. Previously, it had been shown that depression only predicted stroke in cardiac patients, but not in non-cardiac patients. Using the same dataset of the Longitudinal Aging Study Amsterdam (LASA), a population-based cohort study with 9-year follow-up (≥ 55 years), we showed that in non-cardiac patients, depression still predicted incident stroke in those with low neuroticism, but not in those with high neuroticism. The balance between the two different vulnerability factors in late-life depression, neuroticism and (subclinical) vascular disease might be important profiling factors that give an indication of depressive subtype and possible treatment outcome. First results of some small randomised controlled trials, indeed point to better outcome when treatment is focused more specifically on these underlying mechanisms (e.g. Arean et al, 2010).

Overall conclusions

As stated in chapter 1, the main aim of this thesis was to study the association between the late-life depression and subclinical vascular disease, taking into account different depressive symptom clusters and neuroticism. We can conclude that subclinical vascular disease is associated with depressive symptoms in later life. More specifically, depressive symptoms in later life are associated with the metabolic syndrome, obesity and generalised atherosclerosis (hypothesis 1). These associations may in part be explained by increased levels of adipokines, although these associations do not seem consistent for the different adipokines. Furthermore, the somatic-affective symptom cluster of the Beck Depression Inventory drives these associations. Finally, we show the relevance of studying subclinical vascular disease and neuroticism in concert as two different etiological pathways in late-life depression. On the one hand, neuroticism explains less variance in depressive symptoms in the presence of subclinical vascular disease. On the other hand, depression in the absence of neuroticism is suggestive of clinically relevant subclinical vascular disease (hypothesis 2).
Collectively, these studies show the complexity and heterogeneous nature of late-life depression. More attention for specific symptom profiles, as well as the (interplay between the) two major pathways towards late-life depression, may guide clinical decision making, although firm conclusion should be addressed in prospective cohort studies and clinical trials.

**Methodological considerations**

*Study type*
Five of the six studies described in this thesis are based on cross-sectional findings. This limits causal interpretation, as it cannot be determined which of the factors occurred first. Still to date no prospective studies are available relating depressive symptom clusters to obesity, metabolic syndrome, subclinical vascular disease and neuroticism in later life.

*Depressive symptoms versus (major) depressive disorder*
Only one study was confined to a clinical sample of depressed older adults (chapter 4), whereas the five other studies were conducted in population-based samples. In population-based samples, bias toward the healthiest people may have occurred resulting in a lower severity of depressive symptoms as well as a lower severity of atherosclerosis. This may have resulted in less overall variance of the atherosclerosis and depressive symptoms as well as the probability that both characteristics could explain each other.

Depressive symptoms are generally considered on a continuum with depressive disorder; but it is not clear whether this assumption really holds true (Hetrick et al, 2008). Scores on Beck Depression Inventory, as used in this thesis, may reflect common somatic experiences to a certain degree. Many people report symptoms of fatigue or loss of libido, regardless of their medical status. The relative effect of these non-specific symptoms on the overall depressive score is more prominent among people with low levels of depressive symptoms (Thombs et al, 2010). Lower levels of depressive symptoms in the population, as found in the Nijmegen Biomedical Study, might thus be confounded by underlying somatic illnesses (Thombs et al, 2010). Nonetheless, post acute myocardial infarction patients did not have higher somatic symptom scores than psychiatry outpatients and reported, on average, somatic symptom scores only one point higher than under graduate students. (Thombs et al, 2010). Furthermore, 16.7% of the participants in the Nijmegen Biomedical Study scored above the cut-off of 10 on the BDI-I, which is indicative of mild depressive symptoms (Pizzi et al, 2008).
Summary and general discussion

Somatic-affective symptoms: subtype of depression or epiphenomenon of vascular disease

The factor structure of the Beck Depression Inventory (BDI) was used to discriminate between cognitive-affective symptoms and somatic-affective symptoms. As pointed out above, low scores on the BDI may point to non-specific symptoms and this may be especially true for the somatic-affective symptoms (Thombs et al, 2010). Therefore, we cannot exclude the possibility that the association of somatic-affective depressive symptoms with atherosclerosis, obesity and the metabolic syndrome simply reflects underlying somatic illnesses. Nonetheless, also in cardiac patients suffering from a major depressive disorder, only the somatic-affective symptom cluster predicted a negative cardiac prognosis (adjusted for the severity of the heart condition at baseline) (e.g. de Jonge et al, 2006). Furthermore, in older persons suffering from late-life depression, those with significant vascular risk factors indeed had more somatic-affective symptoms compared to depressed older persons without vascular risk factors (Naarding et al, 2007). Having said this, we still cannot be sure that the pathogenesis of somatic-affective symptoms is similar for depressed cardiac patients and depressed non-cardiac patients. This issue deserves more attention in future studies.

In our sample of depressed older adults (chapter 4), the severity of depression was measured with the Inventory of Depressive Symptoms self-report (IDS-SR) (Rush et al, 1996). The IDS, however, has three different dimensions, namely a mood, motivation and somatic dimension (Hegeman et al, 2012). It should be noted that the somatic dimension, however, only include two symptoms. The motivation sub scale was most comparable to the somatic-affective symptom profile of the BDI. Interestingly, the waist circumference was associated with both sum score of the Inventory of Depressive Symptoms (IDS) and the motivation subscale of the IDS (see chapter 4). These findings collectively are in line with a somatic-affective subtype of major depressive disorder.

Atherosclerotic disease

Current hypotheses on the impact of vascular disease on mood regulation include several pathways. Recently, a model has been described that integrates disconnection, inflammation and hypoperfusion processes as causal pathways to vascular depression (Taylor et al, 2013). Vascular disease may contribute to altered brain function characteristic of depression (dorsal hypometabolism, ventral hypermetabolism) either through structural damage adversely affecting connectivity, through perfusion deficits altering regional function, or both. Pro-inflammatory processes increase vascular risk, but may also affect brain function through independent processes. Although we did not assess brain functioning but looked at markers of metabolic risk and generalized atherosclerosis, these conditions probably affect mood regulation by inducing a pro-inflammatory state or by structural damage to mood regulation circuitries of the brain. Nonetheless, none
of these (mediating) pathways have been studied directly. We assessed the Intima Media Thickness (IMT) as a marker for generalized atherosclerosis. It is assumed that the IMT in the common carotid arteries is associated with cerebrovascular disease (Cao et al, 2003). However by including neuroimaging parameters we might have been able to discern between direct effects of atherosclerosis on mood regulation and peripheral effects of atherosclerosis that result in more non-specific symptoms that may overlap with depression, like vital exhaustion and fatigue due to a diminished physical condition.

**Obesity**

Although we have used, beside the Body Mass Index, the most convenient anthropometric indices of visceral adipose tissue (Waist circumference and Waist-to-Hip Ratio) in older people (Villareal et al, 2005), of course Computed Tomography at the level of the fourth lumbar vertebra is the gold standard for quantification of visceral fat (Weber-Hamann et al, 2006). However, anthropometric measures still provide adequate estimates of abdominal fatness and its distribution in men and women aged 55 to 70 years (Stewart et al, 2003).

The amount of abdominal fat as assessed by magnetic resonance imaging (MRI) was highly correlated with the waist circumference (for men r=.60, for women r=.72) and the waist to hip ratio (for men r= 0.71, for women r=.54), whereas the BMI was most strongly associated with overall subcutaneous body fat (for men r=.70, for women r=86) (Stewart et al, 2003).

Visceral fat tissue is metabolically active by the secretion of both pro- and anti-inflammatory cytokines, collectively called adipokines (Trujillo and Scherer, 2006; Milaneshi et al, 2012; Zhao & Stehens, 2013). How these adipokines interact with each other and which adipokines might be specifically linked to depression remains to be elucidated. In our study, we only confirmed an association with NGAL, but not adiponectin. At first, we had chosen to explore the role of adiponectin. In contrast to other adipokines, adiponectin expression is a protective cytokine for vascular health (Matsuzamwa et al, 2011) and several studies have linked adiponectin to depressive symptoms (Wilhelm et al, 2012). Nonetheless, we could not confirm these previous findings. Secondly, we looked at plasma levels of NGAL. This was done because NGAL levels were found to be increased in depressed compared to non-depressed older people (Naudé et al, 2013), animal research offer a biologically plausible explanation for this link (Wang et al, 2007) and finally, NGAL has been identified as an adipokine. Our results, however, should definitively be replicated, preferably in studies testing blood levels and expression in adipocytes of the whole array of adipokines.
Summary and general discussion

Metabolic syndrome

In our study the Metabolic Syndrome (MetS) was defined according to the International Diabetes Federation (IDF) (www.idf.org/webdata/docs/IDF-Meta_def_final.pdf, 2006) as the presence of central obesity (defined as waist circumference with ethnicity specific values; if BMI is > 30 kg/m² central obesity can be assumed and waist circumference does not need to be measured) plus any two of the following four factors: (1) Raised triglycerides (≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality, (2) reduced HDL cholesterol (<40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality, (3) Raised blood pressure (systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension), (4) Raised fasting plasma glucose FPG ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

Another widely used definition of the Metabolic Syndrome is according to the National Cholesterol Education Program Adult Treatment Panel III guidelines as having 3 or more of the following criteria: (1) waist circumference > 102 cm in men or > 88 cm in women; (2) triglyceride level ≥ 150 mg/dL; (3) high-density lipoprotein cholesterol < 40 mg/dL in men or < 50 mg/dL in women; (4) systolic/diastolic blood pressure ≥ 130/85 mm Hg and/or currently using antihypertensive medication; and (5) fasting glucose ≥ 110 mg/dL and/or currently using antidiabetic medication (NCEP, 2002).

The most important difference between the IDF definition and the NCEP definition is that central obesity is mandatory in the IDF definition. On the one hand, this may have strengthened the findings in our studies, since abdominal obesity appears to be the most important component.

Furthermore the cut off of HDL cholesterol for men is lower in the IDF definition (<20 mg/dL vs < 40 mg/dL in NCEP) and the cut off for the fasting glucose is lower (≥100 mg/dL vs ≥ 110 mg/dL in NCEP). Nonetheless, we also looked at the other components of the metabolic syndrome at a dimensional level, thereby overcoming problems due to (arbitrarily) cut-offs of the individual criteria.

Neuroticism

In chapter 6, neuroticism was measured using the Dutch version of the revised Eysenck Personality Questionnaire (EPQ-RSS) (Eysenck & Eysenck, 1975; Eysenck et al, 1985). In chapter 7, neuroticism was measured with the Dutch Personality Questionnaire (DPQ) (Luteijn et al, 1975). Both questionnaires, however, have not been developed for older people and robust cross-validation studies in this age-group are lacking.

In the Longitudinal Aging Study Amsterdam, neuroticism was operationalized by using
a subset of 25 items out of a list of 36 neuroticism items from the Dutch Personality Questionnaire (DPQ; Luteijn, Starren, & van Dijk, 1975, 2000), because the original DPQ scale contained items that were less valid for an aging population and contained too many items for administration in older populations (de Beurs et al, 2000; Smits et al, 1995; Steunenberg et al, 2003). This shortened scale appeared to be a reliable (Cronbach’s a .86) and valid instrument to measure neuroticism in the elderly population (Steunenberg et al, 2003). Total scores range between 0 and 50 and these DPQ items have strong negative relations with the Emotional Stability scale of the Revised NEO Personality Inventory (NEO-PI-R; Luteijn et al, 2000). Moreover, the reliability and stability of neuroticism as measured with the NEO-FFI is good in an older population (Hoekstra et al, 1996).

The EPQ contains items that are less applicable to older persons, like “Would it be interesting for you to use drugs?” and “Do you become irritated by people who drive cautiously?”, as well as items that might be more closely relate to other constructs in later-life, like “Do you often feel lonely?” or “Do you have many friends?”. Nonetheless, a recent study with a follow-up of 37 years in women showed that neuroticism as measured with the Eysenck Personality Questionnaire was relatively stable from mid-life to old-age (Billstedt et al, 2014).

Altogether, these data suggest that neuroticism is a relatively stable construct over the life-span, which can be measured sufficiently reliably in later life (Lucas & Donnellan, 2011) and is not affected by physical health variables (Steunenberg et al, 2005).

A second methodological issue is that we measured neuroticism and depressive symptoms at the same time. The presence of depression amplifies the personality profile of people prone to depression (Costa et al, 2005). However, the relationship between change in personality and change in depressive symptoms is at most moderate (Santor et al, 1997; Marijnissen G et al, 2002; Costa et al, 2005), suggesting that these are not similar constructs.

**Apathy**

Unfortunately, apathy was not directly measured and the relationship between cognitive-affective symptoms of depression and apathy has not been studied in this thesis. It is conceivable that apathy is associated with indifference and lower cognitive activity like rumination, worrying or suicidal thoughts. Nonetheless, the absence of cognitive-affective symptoms is only part of the apathy syndrome (Robert et al, 2009). Apathy as a disorder of motivation that persists over time is defined by consensus and should meet the following requirements: (1) the core feature of apathy, diminished motivation, must be present for at least four weeks, (2) two of the three dimensions of apathy...
(reduced goal-directed behavior, goal-directed cognitive activity, and emotions) must also be present, (3) there should be identifiable functional impairments attributable to the apathy. Finally, exclusion criteria are specified to exclude symptoms and states that mimic apathy (Robert et al, 2009). Our hypothesis of vascular apathy is based only on one component of apathy namely the reduced cognitive activity. Therefore, we cannot exclude the possibility that reduced cognitive activity is discriminative between apathy and depression or just simply reflects their phenomenological overlap.

**Implications for clinical practice**

When translating our results to clinical care, we must acknowledge that most of the results in this thesis are from cross-sectional studies. The cross-sectional design of the studies does not allow our results to be interpreted causally. Therefore, our findings cannot directly be applied in clinical decision making as if they were derived from randomised controlled trials. Still, hopefully, these results will bring the importance of vascular risk factors and subclinical vascular disease into the awareness of clinicians in order to shape or refine their decisions.

In the general population subclinical atherosclerosis and the risk factors visceral obesity and the metabolic syndrome in general may inflate depressive symptoms scores. It may even lead to misdiagnosis of depression in some cardiac patients due to the presence of somatic-affective symptoms that reflect the severity of the atherosclerotic disease but are not part of a formal depressive syndrome, as is implicitly stated by de Jonge and Roest (de Jonge & Roest, 2012).

This could argue for adaptations of the criteria for depressive disorder in patients with atherosclerosis, visceral obesity and the metabolic syndrome with less emphasis on somatic-affective symptoms.

From a clinical point of view, we could argue to differentiate it as a subtype of late-life depression, with specific underlying etiological pathways. Patients suffering from this subtype of depression may benefit from optimising vascular disease-management and treatment programs including physical exercise program like walking or running because this enhances muscle and skeletal strength, decreases obesity and positively affects depression. The other way around, because depression is associated with poorer adherence, interventions for medical problems in patients with atherosclerosis, obesity and metabolic syndrome might benefit from effective concurrent treatment of depression. Altogether, this argues for collaborative care by old-age psychiatrists and specialists in geriatric, internal or vascular medicine.
Back to the case-reports

What can we learn from our studies with respect to the case-reports presented in the general introduction of this thesis? In general, we can conclude that it seems important (but difficult) to differentiate between somatic-affective symptoms, features of sickness behaviour (generally thought to be induced by inflammatory processes) and apathy. Somatic-affective symptoms may point to underlying somatic conditions but may also indicate a depressive disorder. Furthermore, neuroticism and vascular disease should be explicitly evaluated and estimated on the presumed contribution to depressive symptoms in an individual patient. Hereby, it is important to realize that the association between neuroticism and depression may be reduced in the presence of atherosclerosis as well as that the absence of neuroticism increases the risk of clinically relevant subclinical vascular disease.

Mr A, a 68-year-old man, with a history of a late-onset depression three years ago, was presented by the neurologist after a non-fatal stroke with depressive symptoms and inactivity. The main question was whether there was a recurrence of a depressive episode. Probably the occurrence of the first depression was the first marker of his vascular disease burden, as the diagnostic workup showed a serious degree of subclinical atherosclerosis even without clinical vascular disease in history. Retrospectively, the low level of neuroticism of Mr A as well as the first depression at the age of 65 years, would have justified a vascular check-up three years ago.

Mrs B, a 70-year-old woman, who was admitted at the emergency ward of old-age psychiatry with the diagnosis of recurrence of depression. This time, unfortunately, without precipitating event and no recovery after optimising the therapy that had been successful in the past. The main question was how we could explain this depressive episode without precipitating event and without response to treatment. We may postulate that cerebrovascular atherosclerosis had lead to frontostriatal dysfunction and neuropsychological deficits (especially decreased processing speed and executive dysfunctioning). The family of Mrs B already noticed that in the last decade she was less worrisome and anxious. The impact of neuroticism in explaining the late-life depressive symptoms has attenuated. This might be an explanation for occurrence of the depressive episode, more symptoms of apathy, the absence of a precipitating event, and finally, treatment resistance for previously successful treatment strategies.

Mr C, a 55-year-old man, was referred because of depression with prominent symptoms
of fatigue, inactivity, less social involvement and slowness in thinking. The somatic history reported Diabetes Mellitus type 2 and hypertension. On physical examination, we found both hypertension and a pathologically increased waist circumference (125 cm). The main question was whether Mr C was suffering from a late-life depression. Although difficult to differentiate from apathy, Mr C was most likely suffering from a subtype of depression with predominant somatic-affective symptoms and/or a "metabolic depression". Especially in this type of patients, we would suggest to augment traditional treatment of depression with lifestyle training, for example a physical exercise program in order to enhance muscle and skeletal strength and decrease obesity.

Finally miss D, a 84-year-old woman that was seen in a nursing home, refusing to cooperate in rehabilitation after a hip-fracture. She presented with a severe major depressive episode in later life, suffering from depressed mood, feelings of guilt, loss of appetite and underweight. Probably, we see a specific profile of depression in this frail older woman. She might have lost more weight due to comorbid physical frailty, which in itself is associated with depression. Or due to aging she developed some nutritional deficiencies that also have contributed to her depressive symptoms. The severity of her depressive episode and associated weight loss may be typical for depressed older adults presenting in routine psychiatric care, but, as shown in this thesis, may differ from those classified as depressed in population based samples. For these patients, multidisciplinary approach is essential for prioritizing the different problems and treatment components (physical rehabilitation, nutritional intervention, treatment of depression).

**Recommendations for future studies**

Most of the associations found were based on cross-sectional population based research. Acknowledging the age-specific effects we argue for further longitudinal studies specifically in depressed older persons. Such studies might be able to identify depressed subgroups with an unfavourable prognosis with respect to their physical health status. Future cohort studies, however, should be clearly focused in order to measure the most relevant concepts in sufficient detail. First, the whole array of adipokines should be tested as well as the relative impact of the waist circumference assessed with both anthropometric indices and abdominal MR imaging. Secondly, depression should be measured extensively, taking into account the different symptom dimensions of depression as well as other psychological concepts like anxiety, somatization and personality. These concepts should preferably be measured by both self-report scales as semi-structured psychiatric interviews administered by trained mental health professionals. Another
option is to enrich population based cohort studies with a clinical cohort of depressed older patients. Finally, the phenotypic expression of depression, vascular risk factors and peripheral measures of subclinical vascular health should be related to the mood regulating brain circuitries by including neuroimaging and more refined neuropsychological testing.
References


