The weight of subclinical vascular disease & neuroticism in late-life depression
Marijnissen, Radboud

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General introduction
Depression in later life

Major depressive disorders commonly occur in older adults, with a pooled prevalence rate of 1.8% for community-living people aged 55 years and older and a pooled prevalence rate of 9.3% for older persons aged 75 years when institutionalized persons are also taken into account (Beekman et al, 1999; Luppa et al, 2012). The spectrum of depressive symptoms however ranges from mild ‘subthreshold’ conditions to major depression meeting the criteria for a psychiatric disorder (Riedel-Heller et al, 2006; Fiske et al, 2009). Minor depression has been found to be more prevalent in community-dwelling older adults with a prevalence of 9.8% (Beekman et al, 1999) and based on cut-off score on a depression severity measure, clinically relevant depressive symptoms are even more prevalent (respectively 13.5% and 17.1%) (Beekman et al, 1999; Luppa et al, 2012). Depressive symptoms in late life are highly persistent (Luppa et al, 2012). Late-life depression has a chronic course in both the younger elderly (Beekman et al, 2002) as well as the oldest-old (Stek et al, 2006). Moreover, older people have a greater risk of recurrence of depression than younger adults (Licht-Strunk et al, 2007; Mueller et al, 2004).

Depression in later life has been consistently associated with negative consequences irrespective of whether depression is defined as depressive symptoms, minor or subthreshold depression or major depressive disorder. One may thus ask whether the diagnostic cut-off applied in the classification system DSM-IV (Diagnostic and Statistical Manual for Mental disorders) is specifically-tailored enough for late-life depression. These negative consequences include a higher incidence of several age-related diseases like cardiovascular disease, stroke, diabetes and obesity morbidity (Penninx et al, 2013), functional decline and even a higher mortality rate. Not surprisingly, late-life depression is associated with a poorer self-rated health and decreased quality of life. From a societal perspective, increased days lost due to disability (Beekman et al, 1995; Fiske et al, 2009) and increased health care utilization and direct costs (Katon et al, 2003; Luppa et al, 2008), probably due to experiencing functional disability and cognitive decline (Dombrovski et al, 2007; Lenze et al, 2005) can not be neglected. A complicating factor in clinical care, however, is the diversity in symptoms, presumed pathophysiological mechanisms and consequences for that individual depressed patient we see in our practice. Accumulating evidence show that depressive disorder is a heterogeneous condition with respect to its phenomenology as well as its underlying pathophysiological mechanisms (Shafer, 2006; de Jonge et al, 2006; Wardenaar et al, 2010; Ormel & de Jonge, 2011). This heterogeneity is assumed to increase with advancing
age and when taking subthreshold forms of depression into account. This thesis is devoted to further unravel heterogeneity with respect to symptom profiles of depressive symptoms in relation to two major pathways leading to late-life depression, i.e. vascular disease burden and neuroticism.

Phenomenological heterogeneity: Depressive symptom profiles

The DSM-classification system has specified several subtypes of depressive disorder, based on severity, course or actual symptoms. Based on the severity of actual symptoms, depressive disorder may be specified as mild, moderate or severe and based on the symptom profile further specified as with anxious distress, mixed features, melancholic features, atypical features, catatonia or psychotic features. Nonetheless, these severity specifiers may only be applied when a patient meets the general criteria of a depressive episode. This is made possible by applying a polythetic definition (that is a patients needs to satisfy some but not all symptoms) as well as by defining individual criteria in two directions (for example psychomotor retardation versus agitation, weight loss versus weight gain).

Irrespective of this diversity, several observer-rated and self-rated instruments have been developed to measure the severity of depression. As can be expected, factor analyses of these questionnaires often show two or more dimensions (e.g. Beck & Steer, 1987; de Jonge et al, 2006). For example, the most often-used depression severity instrument, the Hamilton Depression Rating Scale, appears to be multidimensional. A large study on depressed outpatients identified four subscales, referring to 1) somatic anxiety, 2) psychic anxiety, 3) core depressive symptoms and 4) anorexia (Pancheri et al, 2002), although several other solutions have also been reported (e.g. Bech et al, 1981). In this thesis, symptom profiles will be based on the Inventory of Depressive Symptoms self-report (IDS-SR) and on the Beck Depression Inventory (BDI). The IDS-SR is an increasingly-used instrument that covers both the key symptoms of depression and somatic/vegetative symptoms, originally developed to measure severity of overall depression (www.idsqids.org) (Rush et al, 1996). In a sample of depressed older persons, three dimensions have been identified, including a mood, a motivation and a somatic dimension (Hegeman et al, 2012). The BDI is one of the most frequently used self report instruments to assess depressive symptoms and its factor structure has often been examined, mostly resulting in two (Beck and Steer, 1987) or three dimensions (Morley et al, 2002; de Jonge et al, 2006).
Pathways to late-life depression

Two prospective predictors of late-life depression are neuroticism (Steunenberg et al, 2006) and vascular disease (Taylor et al, 2013; Valkanova & Ebmeier, 2013). In the past decade, most research has focused on the role of vascular disease (Sneed et al, 2008; Ormel & de Jonge, 2011; Taylor et al, 2013), whereas neuroticism has less frequently been investigated in old age psychiatry. Both (major) pathways may act to a certain degree in individual patients. In this thesis, the vascular pathway will be examined with respect to subclinical vascular disease and also in interaction with neuroticism.

Vascular depression and subclinical vascular disease

In 1997 Alexopoulos and colleagues (Alexopoulos et al, 1997) and Krishnan and colleagues (Krishnan et al, 1997) independently postulated the ‘vascular depression hypothesis’ stating cerebrovascular disease may predispose, precipitate or perpetuate some geriatric depressive syndromes. The group of Alexoupoulos substantiated this hypothesis primarily with epidemiological findings on the (reciprocal) relationship between vascular disease and depression and a late-onset depressive subtype. Krishnan and colleagues substantiated this hypothesis on an increased severity of white matter hyperintensities (WMH) in depressed compared to non-depressed older persons seen on T2-weighted or fluid-attenuated inversion recovery MRI (Coffey et al, 1989). In patients with late-life depression, these WMH are presumed to be of ischemic origin due to its association with cerebrovascular risk factors, including diabetes, cardiac disease and hypertension (Thomas et al, 2002; Taylor et al, 2005; Mast et al, 2008; Goodman et al, 2008; Taylor et al, 2013). In general, the phenomenological expression of vascular depression is characterised by apathy, psychomotor retardation, cognitive deficits, lack of insight and disability disproportional to the depression severity (Taylor et al, 2013), whereas a low mood and feelings of guilt or worthlessness are less pronounced. This might be explained by ischemic damage to specific white matter fiber tracts, including the cingulum bundle, uncinate fasciculus and superior longitudinal fasciculus (Sheline et al, 2008; Dalby et al, 2010; Taylor et al, 2011) leading to executive function deficits in neuropsychological testing (Smith et al, 2011) and apathy and loss of interest as clinical features (Esposito et al, 2010). In its most advanced form, vascular depression would approximate post-stroke depression (Aben et al, 2002). Further refinement of the vascular depression hypothesis has culminated in a depressive-executive dysfunction syndrome (Alexopoulos et al, 2001). Until now, the evidence for a real distinctive disorder remains limited with many inconsistent results (Baldwin et al, 2005).
Thus far, epidemiological studies on vascular depression classify people as vascular compromised in case of cerebro- and/or cardiovascular events. These studies thereby ignore the fact that many older people do have significant subclinical vascular damage reflected in increased levels of vascular risk factors (e.g. metabolic syndrome) and significant atherosclerosis throughout the body. Atherosclerosis is a gradual process, which already starts in early adolescence and may remain asymptomatic for decades before the manifestation of clinical events at later age (Ross, 1993). To date, the association between subclinical vascular disease and depression has hardly been examined. In this thesis, we focus on the association between different depressive symptom dimensions on the one hand and atherosclerosis, metabolic syndrome and obesity on the other hand. Since patients with obesity, metabolic syndrome and/or advanced levels of atherosclerosis do not necessarily have experienced a vascular event, we use the term subclinical vascular disease collectively for obesity, metabolic syndrome and/or atherosclerosis in the introduction and summary of this thesis.

Atherosclerosis will be based on the carotid intima-media thickness (cIMT). The cIMT can be measured noninvasively by ultrasonography (O’Leary et al, 2002). CIMT is an established marker for subclinical atherosclerosis and an independent predictor for cardiovascular risk (van den Oord et al, 2013). Whether the cIMT is associated with depression remains to be elucidated as both positive (Tiemeier et al, 2004; Elovainio et al, 2005) and negative results (Ohiraa et al, 2012) have been reported. One may hypothize that this association only exists with specific depressive symptom profiles, which may not be assessed properly or masked in some studies.

The metabolic syndrome (central adiposity, abnormal glucose regulation, elevated triglycerides, lowered high-density lipoprotein cholesterol and elevated blood pressure) (Alberti et al, 2009) is associated with subclinical atherosclerosis in young, middle-aged and older adults (Hulthe et al, 2000; Kullo et al, 2005; Tzou et al, 2005; Bertoni et al, 2007; Chirinos et al, 2014). There is an association between depression and the metabolic syndrome (Koponen et al, 2008; Akbaraly et al, 2011; Pan et al, 2012) as well as with its individual components like impaired glycemic control (Gale et al, 2010). Waist circumference seems the most important metabolic syndrome feature in relation to depression in older persons (Vogelzangs et al, 2011). Meta-analysis of cross-sectional studies confirmed a significant association between depression and body mass index as index for obesity (de Wit et al, 2010) and meta-analyses of longitudinal studies found depression as a risk factor for weight gain, as well as body mass index as a risk factor for the development of depression (Luppino et al, 2010). Obesity as risk factor for clinical cardiovascular diseases, however, seems specifically related to anthropometric measures of abdominal adiposity, such as waist hip-ratio (WHR) and waist circumference (Yan et al, 2009). Atherosclerotic progression is accelerated by abdominal obesity (Yan et
al, 2009; Chagas et al 2011). A likely explanation lies in the fact that visceral fat is metabolically active by the secretion of inflammatory cytokines, collectively called adipokines.

**Neuroticism**

Apart from cardiovascular disease (Taylor et al, 2013; Valkanova et al, 2013), neuroticism is also a major vulnerability factor in late-life depression (Steunenberg et al, 2006; Kendler at al, 2006). Neuroticism refers to the personality trait of being sensitive to negative stimuli (Tellegen et al, 1985), causing emotional instability and negative moods like anxiety, sadness, guilt, hostility and self-dissatisfaction (Watson & Clark, 1984; Steunenberg et al, 2007). In depression, the cognitive-affective symptoms, like worrying or suicidal thoughts, may be more specifically associated with neuroticism. Cognitive reactivity (i.e. the ease with which particular patterns of negative thinking are reactivated in response to low mood) mediates the predisposing effects of neuroticism to depression (Barnhofer et al, 2010; Boyle et al, 2010). The typical or melancholical depression subtype is characterized by a combination of stressful life events and vulnerability of personality characteristics in the domains of neuroticism and stress sensitivity (Kendler at al, 2002; Ormel et al, 2001; Ormel et al, 2004; Hettema et al, 2006).

Neuroticism is one of the most well established dimensions in the ‘Big Five’ (Costa & McCrae, 1994) and is strongly related to mental and physical health, level of social support, self-rated health and functional limitations (Siegler & Brummet, 2000; Smith & Gallo, 2001; Duberstein et al, 2003). In line with the stability assumption (Costa & McCrae, 1994; Costa et al, 2000; Martin et al, 2002; Maiden et al, 2003), neuroticism remains rather stable in old age and is independent of physical illness and functional limitations (Steunenberg et al, 2005). A higher level of neuroticism predicts chronicity of depression in later life with an effect-size comparable to the negative impact of physical health and even stronger than the negative impact of cognitive decline or loss of social resources (Steunenberg et al, 2007). Finally, a high level of neuroticism is a strong predictor of recurrence (Surtees et al, 1996; Steunenberg et al, 2009; Steunenberg et al, 2010). In this thesis, the interaction between vascular disease burden and neuroticism will be explored, taking depressive symptom profiles into account.

**Towards integration of subclinical vascular disease, neuroticism and depressive symptom profiles**

Recently an integrative model of the relationships between depression and the prognosis of coronary artery disease (CAD) was postulated (Ormel & de Jonge, 2011). The model
hypothesizes that CAD, with its underlying atherosclerosis, is a risk factor for somatic-affective depression but less so for cognitive-affective depression. This hypothesis is primarily based on findings with the Beck Depression Inventory (BDI) for which two dimensions are found consistently in depressed cardiac patients (a cognitive-affective and a somatic-affective dimension) and less consistently a third dimension (appetitive) (de Jonge et al, 2006; Linke et al, 2009). Subclinical atherosclerosis might affect the risk of somatic depression by the involvement of systemic inflammation (Frasure et al, 2007; Glassmann et al, 2007) long before the diagnosis of CAD. In a large sample of older primary care patients initially free of CAD diagnosis it was found that the longitudinal relationship between overall depressive symptom severity and incident CAD events might be driven primarily by the somatic symptom dimension of depression (Hawkins et al, 2014).

Neuroticism and cardiovascular disease, as major risk factors for late-life depression, have hardly been examined in relation to each other. A small case-control study found a negative interaction between vascular risk and psychosocial vulnerability for depression (Oldehinkel et al, 2003). In older people aged 70 years and older, the effect of neuroticism on explaining depressive symptoms was attenuated by the presence of cerebrovascular disease (Wouts et al, 2011).

Two aspects will be elaborated in the present thesis.
• Firstly, based on the above, a hypothesis may be that depressive symptoms, especially the somatic-affective symptoms, may simply be symptoms of an underlying somatic disorder. This may explain why subthreshold forms of depression, often consisting of primarily somatic-affective symptoms, are related to negative health outcomes.
• Secondly, although the findings in literature till so far about the interaction between neuroticism and cardiovascular disease may have been chance findings or ceiling effects of two important risk factors, one also may hypothesize that cerebrovascular disease causes apathy that in turn decreases the effect of neuroticism on depression. Cerebrovascular damage leads to fronto-striatal dysfunction and neuropsychological deficits, especially decreased processing speed and executive dysfunctioning, that are more specifically linked with apathy than with depressed mood per se. This apathy may lead to less impact of neuroticism on late life depression.

Both of these hypotheses will be explored in this thesis. Before we do so, a few case reports will be presented that illustrate the clinical relevance of these questions.
Some case-reports

Case description A
Mr A, a 68-year-old man was seen in consultancy because of depressive symptoms and inactivity. The patient had developed a non-fatal stroke and a diagnostic workup by the neurologist showed a serious degree of subclinical atherosclerosis, even without clinical vascular disease in history. His medical history reported one depressive period prior to the non-fatal stroke but no cardiac or cerebrovascular disease. He suffered from the first episode of a major depressive disorder three years ago in the absence of either precipitating circumstances as predisposing characteristics. He did not report any life-event prior to this episode and there was no evidence of instable personality traits. He said to be happily married, to be father of three successful children and to have enjoyed two years of his retirement after a satisfying job as a construction worker. The general practitioner had treated his depression successfully with paroxetine combined with some sessions of problem solving therapy. To the patient’s opinion the depressive symptoms were fully in remission after treatment. His wife, however, was not fully convinced, as symptoms of ‘fatigue’ existed and he did not enjoy sea fishing with his friends anymore. Psychiatric examination showed a moderate depressed mood, reduced initiative, psychomotor retardation and signs of executive deficits.

Should we conclude there was a recurrence of a depressive episode? Could the occurrence of his first depression have been the first marker of his vascular disease burden? Would this possibility have warranted a vascular check-up in this case?

Case description B
Mrs B, a 70-year-old woman was admitted at the emergency ward of old-age psychiatry with the diagnoses of Major Depressive Disorder. She had a history of recurrent depressive disorder. From her 26th till 59th she had been admitted four times. Always there had been precipitating circumstances (birth of a child, loss of her mother, moving to another part of the country, worrying about her children). During the admissions a recurrent depressive disorder in a woman with neurotic personality traits was diagnosed. The major depressive episodes always remitted fully by a tricyclic antidepressant (amitriptyline or nortriptyline) in combination with cognitive therapy. Beside her psychiatric history there was no somatic history except backache and headache without a somatic explanation and at the age of 57 she developed hypertension. Because of this diagnosis of hypertension, she quit smoking.
Before the current admission there were no precipitating circumstances. In fact, according to her husband and children, she had been less worrisome and anxious during the last decade. She had continued using nortriptyline, prescribed by the general practitioner. In the last year she developed more depressive symptoms. She was tired, lost appetite and weight; she became dramatically preoccupied with physical sensations and developed insomnia. The weeks before submission she was sad, cried a lot and was very irritated towards her husband. Psychiatric examination suggested a depressed mood and decreased speed in thinking. She was preoccupied by her somatic complaints. Physical and laboratory tests revealed no abnormalities. The Montgomery Asberg Depression Rating Scale (MADRS) score was 30. A Major Depressive Disorder was diagnosed. During admission cognitive therapy was restarted and the nortriptyline level appeared not be adequate, so the dosage was elevated to get an optimal level. After 6 weeks there was no remission; addition of lithiumcarbonate in adequate dosage also had no effect.

How can we explain that this episode occurred without precipitating events and why did she not recover after optimising the drug therapy that had previously and repeatedly been successful?

Case description C
Mr C, a 55-year-old man, was referred by the GP because of a depression. His psychiatric history included a posttraumatic stress disorder after a car accident, which has been successfully treated with Eye-Movement Desensitisation Reprocessing (EMDR). His somatic history was limited to diabetes mellitus type 2 and hypertension. The daughter was psychiatrist herself and advised her father to see a colleague psychiatrist because she doubted the GPs diagnosis of depression.

Mr C himself did not have many complaints. He felt a little bit fatigue but reported to be still socially involved. Nonetheless, he was taking more rest at home, which has resulted in conflicts with his wife because of his inactivity. Feelings of guilt were only present when his wife confronted him with his inactivity. He was happily married although his wife became frustrated by the depressive symptoms of Mr C. Until 8 months ago he worked as a teacher on a primary school in the village where he lives. He had always been a popular man in the village; beside his work he was active in the musical society where he plays tuba. The last year, he increasingly skipped his weekly meetings without any apparent reasons. This was obvious to his wife because Mr C always liked the social aspects of the meeting, talking to other musicians and sharing a drink. Psychiatric examination revealed inactivity, some slowness in thinking and a dysphoric
mood. Physical examination showed beside a hypertension of 170/100 mmHg and an obvious potbelly with a waist circumference of 125 cm, no abnormalities. Laboratory tests only showed elevated triglycerides. As medication he used fosinopril, metformin and simvastatin.

Is Mr C indeed suffering from a late-life depression? Or was the presumption of his daughter right and does Mr C suffer from a specific subtype of late-life depression, i.e. a ‘metabolic depression with prominent somatic-affective depressive symptoms and few cognitive-affective symptoms’? Or does Mr C suffer from apathy?

Case description D
Miss D, an 84-year-old woman was seen in a nursery by a consultant psychiatrist. After an operation for hip-fracture and admission at a geriatric traumatology ward, she was referred to the nursery. The psychiatric history showed a depression at the age of 23 after a girl friend had committed suicide. She had been physically healthy all of her life. The reason for consultation was that the rehabilitation was not going well because she refused to cooperate with the nurses and physiotherapist. To the nurses, miss D appeared to be exhausted, but her doctor found no explanation for this in physical and laboratory tests. Miss D complained about sadness, worrying about the future, loss of appetite, weight loss during the last 8 months and insomnia. Her nephew mentioned that miss D has always been an active woman. She has never been married and worked as a tour guide in Asia and Africa. After retirement she did some work as a local tour guide in the city centre. She was a great aunt for all her nephews and nieces, a very social woman. She visited her family often, loved knitting and stitching, gardening and played bridge. In fact she was active till Christmas two years ago, when she increasingly worried about recently emerged family conflicts. She became more and more inactive, lost weight, felt very weak and fell at least twice a month without a reason. It was very frustrating for her to become dependent. In psychiatric examination an underweight woman was seen with an obvious slowness and indeed she made an exhausted impression. She was preoccupied with guilt and frustration about her dependency. She was dissatisfied with the admission in the nursery; there was no future for her. The mood was extremely sad.

Is this a classical normal depression? Should we expect a specific profile in a frail older woman?
Aims and outline of this thesis

The main aim of this thesis is to study the association between the late-life depression and subclinical vascular disease, taking into account different depressive symptom profiles and neuroticism. More specifically, we formulated the following hypotheses:

1. Subclinical vascular disease is associated with late-life depression:
   a. Metabolic syndrome is associated with late-life depression
   b. Obesity is associated with late-life depression
   c. Generalised atherosclerosis indexed by the intima media thickness (IMT) of the carotid artery is associated with late-life depression

2. Subclinical vascular disease, more specifically metabolic syndrome, obesity and IMT are particularly associated with the somatic-affective symptom cluster in depression.

3. (Subclinical) vascular disease and neuroticism represent two different etiological pathways in late-life depression.

Figure 1  Associations tested in this thesis (numbers refer to chapter numbers).
Part one: Metabolic syndrome and obesity

Part one of this thesis focuses on the association between depressive symptom profiles and metabolic syndrome. Particular attention is paid to the abdominal obesity as central component of the metabolic syndrome and its metabolic activity.

In chapter 2 we describe the association between the metabolic syndrome and its individual components and depressive symptoms using baseline data of the Nijmegen Biomedical Study (NBS). The associations are studied in middle aged and older persons (50 - 70 years) living in the community. One important limitation of previous studies on the association between the metabolic syndrome and late-life depression is examined in more depth, namely the subtyping of depressive symptoms, including somatic-affective symptom cluster and cognitive-affective symptom cluster based on the Beck Depression Inventory. As visceral fat tissue is metabolically active by the secretion of cytokines, as mentioned before collective called adipokines, which may contribute to the negative health effect of obesity. We will explore the association between depression and adiponectin, as this has been linked to mood regulation, although results are mixed (Lehto et al, 2010; Diniz et al, 2012; Jeong et al, 2012). In contrast to other adipokines, adiponectin is a protective cytokine for vascular health and lowered concentration have been demonstrated in visceral obesity, insulin resistance, diabetes mellitus, metabolic syndrome and hypertension independent of the body mass index (Mathieu et al, 2009; Taylor et al, 2010; Zeugmann et al, 2010; Matsuzawa et al, 2011; Yadav et al, 2012).

In chapter 3 we will focus on probably the most important component of the metabolic syndrome in the association with depression, obesity. Two important limitations of previous studies on the association between obesity and late-life depression are examined in more depth. First, the use of different measures of obesity, including Body Mass Index, Waist-Hip ratio and waist circumference. Secondly, the subtyping of depressive symptoms, including somatic-affective symptom cluster and cognitive-affective symptom cluster based on the Beck Depression Inventory.

Chapter 4 addresses the association between late-life depression and waist-circumference in an older (≥60 years) clinically depressed sample from the Netherlands Study of Depression in Older persons (NESDO). This enabled us to explore several characteristics of late-life depression like age of onset, comorbidity with dysthymia and duration of illness in addition to symptom profiles based on the Inventory of Depressive Symptoms in the association between depression and obesity. In this paper, we also examine the role of Neutrophil Gelatinase-Associated Lipocalin (NGAL), an inflammatory marker recently identified as an adipokine (Huang et al, 2012).
**Part two: Atherosclerosis and neuroticism**

In part two we focus on (subclinical) atherosclerosis and neuroticism as two of the major risk factors of late-depression.

In chapter 5, we first describe a study into the relationship between (subclinical) atherosclerosis, measured by the intima media thickness (IMT), and depressive symptom clusters within the Nijmegen Biomedical Study (NBS). Hereby, we extend previous studies showing an association between atherosclerosis and depression in general. In chapter 6, we further explore these associations by examining the interaction between subclinical atherosclerosis and neuroticism with regard to explaining variance in both somatic-affective depressive symptoms and cognitive-affective depressive symptoms.

Finally, in chapter 7, neuroticism and vascular disease are examined in a community sample age 55 years and over taken from the Longitudinal Aging Study Amsterdam (LASA). The findings in chapter 5 and 6 culminate in the hypothesis that two separate groups of patients with late-life depression can be discerned based on aetiological ground, a neuroticism-associated and vascular depression. We hypothesise that patients with subclinical vascular disease are at increased risk for stroke, whereas those suffering from neuroticism-associated depression are not. Therefore we will examine whether or not subjects with low levels of neuroticism do indeed have an increased risk of stroke in patients free of vascular events.

In chapter 8 the main findings of these studies are reviewed, methodological considerations and the clinical implications for the elderly depressed patients are discussed.
Appendix

In this thesis, three different data sets were used derived from three studies: two population based studies and one clinical cohort study including patients suffering from late-life depressive disorders.

**Nijmegen Biomedical Study (NBS)**

The Nijmegen Biomedical Study is a population-based survey conducted in Nijmegen of people aged 20-90 years. In the year 2000 the NBS was initiated among the inhabitants of the municipality of Nijmegen by the departments of Epidemiology, Biostatistics and HTA, Clinical Chemistry, and Endocrinology of the Radboud University Nijmegen Medical Centre (RUNMC). Age- and sex-stratified randomly selected adult inhabitants of Nijmegen (n =22 452) received an invitation to fill out a postal questionnaire on lifestyle and medical history. A total of 9371 (41.7%) recipients responded to the questionnaire (Hoogendoorn et al, 2006; Holewijn et al, 2010).

For the studies presented in this thesis a sample was drawn from the NBS. In 2004 and 2005 a questionnaire was sent to all participants (N=2807) aged 50 to 70. Of these persons 1517 (54%) gave additional informed consent to participate in a study on non-invasive measurement of atherosclerosis. These participants visited the hospital for a detailed assessment of atherosclerotic disease and its risk factors and consequences.

**Netherlands Study of Depression in Older Persons (NESDO)**

The Netherlands Study of Depression in Older Persons (NESDO) is a multi-site naturalistic cohort study, aims to examine the course and consequences of depressive disorders in older persons. From 2007 until 2010 the NESDO consortium has recruited 378 depressed and 132 non-depressed older persons aged 60 through 93 years. Recruitment of depressed older persons took place at five regions in the Netherlands from both mental health care institutes and general practitioners in order to include persons with late-life depression in various developmental and severity stages. The comparison group of non-depressed persons was recruited at the same general practices that recruited patients. A random sample of older people who scored less than four on the Geriatric Depression Scale during a visit to their GP was asked informed consent. (Comijs et al, 2011)

For the present study we used the baseline assessment of the NESDO. The baseline assessment included written questionnaires, interviews, a medical examination, cognitive tests and collection of blood and saliva samples. Information was gathered about mental health outcomes and demographic, psychosocial, biological, cognitive and genetic determinants.
**Longitudinal Aging Study Amsterdam (LASA)**
The Longitudinal Aging Study Amsterdam is a prospective cohort study of Dutch people aged 55 to 85 years (n=3107). LASA started in 1992 and the general aim of LASA was to study the autonomy and well-being of an aging population. A randomly selected age- and sex-stratified sample (according to expected mortality figures) was drawn from the population registers of 11 municipalities in the Netherlands. The reason for this relative oversampling of men and oldest-old people (both men and women) was to compensate for an anticipated higher unavailability for follow-up among the older-old and men. The sample first took part in the cross-sectional NESTOR–living arrangements and social networks study and was later interviewed and followed up every 3 years in LASA. Of the NESTOR–living arrangements and social networks study sample, 81.7% of the persons also participated in LASA (non-response was related to age but not to sex). All interviews were tape-recorded for quality control purposes. (Beekman et al, 1995; Huisman et al, 2011).

For the study presented in this thesis, we used data up to 9 years of follow-up and included only those LASA participants, in whom neuroticism was evaluated at baseline, leaving a total study sample of 2050 participants.
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Part one

Metabolic syndrome and obesity