Chapter 7

SUMMARY AND GENERAL DISCUSSION

NEDERLANDSE SAMENVATTING
7.1 INTRODUCTION

Disturbances in gait, cognition and mood are frequently seen in old age. These symptoms are frequent chief complaints of older patients. They lead to impairments of independent functioning and affect quality of life. Knowledge about their interplay and underlying pathologies may help to maintain and restore health in older people. In this thesis the relationship between different aspects of slowing with depression, pain, cognitive decline, falls and mortality was investigated.

In this chapter the findings of the previous empirical chapters will be summarized. Successively, putative underlying mechanisms for slowing will be discussed, as well as the clinical value that slowing can have in the context of older people with and without depressive symptoms. Successively, it will be argued whether slowing can be regarded as a geriatric syndrome. Then some methodological issues will be described. The chapter will end discussing recommendations for future research and therapeutic interventions. But first, I will give a summary of the findings.

7.2 SUMMARY OF FINDINGS

Depression is common in late life with prevalence rates for major depression and subthreshold depression of 1 to 4% and 8 to 16% in community samples respectively. Importantly, the prognosis of depression is worse in older people when compared with adults, with a chronic course in more than 50% as opposed to 10 to 30% in adults. A worse prognosis might be explained by a higher prevalence of known risk factors for chronicity in older people, such as bereavement, social isolation and functional limitations. However, specific age-related pathology related to cognitive decline might account for the poorer prognosis, as prevalence rates of co-morbid depressions are high in patients with Mild Cognitive Impairment (MCI), Alzheimer disease and stroke. Moreover, late life depression has been shown to be associated with vascular brain damage. Therefore, cognitive decline may mark a specific course type of late life depression. When interpreting an association between cognitive impairment and depression, it might be important to distinguish different domains of cognition, since impairments in any of these could have a differential impact on the course of late life depression. In chapter two it was investigated therefore, whether specific domains of cognitive functioning predict the natural course of depressive symptoms in older people. It was demonstrated that slowed processing speed was the only cognitive domain associated with a poor natural course of depressive symptoms in older people. This association was not explained by risk factors for vascular brain damage or CVA.
Other cognitive domains such as global cognitive functioning and memory tasks were not associated with a worse prognosis of depressive symptoms. From the results it is concluded that when dealing with clinically relevant depressive symptoms in an older person with comorbid cognitive impairment, processing speed is a more useful tool than the MMSE in predicting the prognosis.

Gait speed, being one of the features of gross motor activity in mood disorders, can be reliably and easily assessed in older individuals living in the community. Gait speed is associated with cognitive decline, falls, institutionalization and mortality, but its relevance with regard to the natural course of late life depression was not explored before. After having demonstrated the importance of slowed processing speed in the prognosis of depressive symptoms in chapter two, in chapter three it was hypothesized that also slowed gait speed predicted chronicity of depressive symptoms in a community-based population of old people with depressive symptoms. As gait speed may be a marker of several underlying pathophysiological factors that contribute to the persistence in late life depression, a number of those factors was tested. In this study it was demonstrated that slowed gait speed did predict chronicity of depressive symptoms. This association was independent of processing speed and of (risk factors for) vascular diseases, somatic comorbidity, and of a marker for chronic inflammation. It is concluded that slowed gait speed operates through a different mechanism than slowed processing speed in its association with chronicity of depressive symptoms. Also, slowed gait speed in these respondents does not point at a specific underlying pathology.

Diseases that can explain slowed gait and processing speed include stroke, arthritis or joint deformities, chronic lung disease, and cardiac diseases. In chapter two and three it was demonstrated that slowed processing speed and slowed gait speed are associated with depressive symptoms with a chronic course, independent of confounding factors, somatic diseases and risk factors for vascular brain damage. Late life depression with a chronic course is thus one of the specific diseases that may explain slowing in a geriatric patient.

While cross-sectional studies have demonstrated the frequent co-occurrence of gait speed and depressive symptoms, longitudinal studies are needed to clarify the direction of this association and to ascertain whether gait speed impairment and depressive symptoms share common aetiologies. Should both phenomena indeed be part of a common underlying pathology, preventive measures aimed at this pathology would reduce the risk of older people developing a slower gait or depressive symptoms. Separate measures should be taken if depressive symptoms and slowed gait each have
their own underlying pathology. The data of chapter two and three were generated in respondents with depressive symptoms. To ascertain whether the incidence of gait speed impairment and depressive symptoms share common aetiologies and to clarify the direction of such an association, in chapter four the temporal association between slowed gait and depressive symptoms was investigated in respondents with and without depressive symptoms. Slowed gait speed independently predicted depressive symptoms in men. In women, a bidirectional association was found between gait speed and depressive symptoms in univariate analyses only; these bidirectional associations were not explained by same covariates. These results suggest that depressive symptoms and slowed gait speed in late life originate from different pathologies, both of which require their own treatment strategies. The temporal association in men has important practical implications: a slowed gait in non-depressed older men should be a reason to be alert not only to somatic health threats, but also to the development of depressive symptoms.

In chapter five a side step to pain was made. Population-based studies among older people consistently demonstrate that both pain and depression are highly prevalent in late life. The co-occurrence of pain and depression is associated with worse clinical outcomes than either condition alone. This interaction between pain and depression has been labelled by some as the depression-pain dyad. With an increasing number of comorbidities occurring with aging, a better understanding of the link between pain and depression may identify factors suitable for prevention or improved treatment outcomes.

When studying age-related aspects in the co-occurrence of depressive symptoms and pain, the incorporation of frailty over chronological age can yield additional information, since frailty can be regarded as a measure of biological aging. Whether the pain-depression dyad is different in frail and non-frail old people has, to our knowledge, never previously been investigated. The primary aim of the study was to investigate the effect of age and aging on the association between pain and depression over 13 years. A strong association was demonstrated between pain and depressive symptoms over this period. Moreover, this association remained unaffected by follow-up time, by age or by frailty status. Forty percent of the longitudinal association was explained by measured somatic comorbidity and psychological factors. It was concluded that neither aging nor frailty influence the pain-depression dyad over time, while well-known factors partly explain their intimate association in older age. Our study is a strong argument not to withhold any effective somatic or psychological treatment in patients suffering from both pain and depressive symptoms, irrespective of age or frailty status.
In chapter six it was examined whether gait speed and processing speed predict adverse health outcomes, both individually and in concert. Processing speed is a cognitive measure of hierarchical importance for other cognitive domains and it declines with aging.\textsuperscript{20} Like gait speed, processing speed is associated with future morbidity and mortality.\textsuperscript{21,22} Both slowing symptoms may originate from one underlying pathology, as it has been demonstrated that processing speed mediates the association between slowed gait speed and a decreased cerebral prefrontal volume.\textsuperscript{23,24} These findings suggest that gait speed and processing speed may form a pair of slowing markers with unique clinical prognostic abilities. However, until now there have been no studies investigating the combined predictive potential of these two slowing symptoms for various adverse health outcomes, while also from clinical observation it appears that the individual exhibiting a combination of both slowing symptoms is at greater risk for adverse health outcomes than the individual showing only one slowing symptom.

As outlined previously, psychomotor slowing is a cardinal feature of late life depression. It is therefore hypothesized that depressive symptoms mediate the association of both slowing symptoms with adverse health outcomes. Additionally, we were interested to know whether the predictive ability of the slowing symptoms differed for people with and without depressive symptoms, as this would be an argument for specific interventions in slow older people with or without depressive symptoms. It is demonstrated that processing speed predicts persistent cognitive decline (PCD), slowed gait speed predicts falls, and both slowing symptoms predict mortality. For falls there was an interaction between the two slowing symptoms; only in respondents with a slowed gait, slowed processing speed predicted falls. A slowing sum score, which combined both slowing symptoms, predicted all three outcomes. Moreover, it showed a linearly and strong association with mortality suggesting an additive effect of its two components. Depressive symptoms did not mediate or moderate any of the associations. Our results demonstrated that slowing of gait and slowing of thought predict several adverse health outcomes in old age. The results demonstrated the importance to include both gait and processing speed in research and clinical practice with older people. The presence of both slowing symptoms was strongly associated with mortality, suggesting a final common pathway with separate functional trajectories. We conclude that processing speed is at least as relevant as gait speed as predictor of adverse health outcomes in late life.

Concluding this paragraph, I would like to refer to Figure one of chapter one., where possible associations and underlying mechanisms are depicted. It is demonstrated that both slowing symptoms are associated with a specific course of depressive symptoms and this association is not explained by any underlying mechanism tested. Both slowing
symptoms mark a chronic subtype of late life depression, but it is also possible that the slowing symptoms and depressive symptoms reinforce each other once the co-occur in one individual. With regard to the bidirectional association of the incidence of slowing of gait speed and of depressive symptoms a different picture emerges. Here the results suggest that the bidirectional association is at least in part dependent upon co-variates. In paragraph 7.5 clinical consequences of these observation will discussed. Finally, it is demonstrated that pain and depressive symptoms are intimately associated over time, their association is partly explained by well-known somatic and psychological factors and this association is not moderated by gait speed. Geriatric medicine is about co-morbidities on different domains. As discussed above, the findings of chapter five can guide health workers when confronted with a frail older patient suffering from the combination of somatic morbidity, specific personality traits, depressive symptoms and pain.

7.3 SLOWING AS GERIATRIC SYNDROME

Slowing of gait and cognition are main features in daily geriatric practice. In this paragraph it will be argued that the findings of this thesis (chapter two, three and six) demonstrate that slowing can be seen as a geriatric syndrome.

A geriatric syndrome is characterized by a set of symptoms that are highly prevalent in old age, in which the leading symptom is linked to a number of aetiological factors or diseases in other organs.25 Geriatric syndromes are associated with adverse health outcomes.26 As geriatric syndromes are linked to diseases and risk factors for adverse health outcomes, the diagnostic workup of geriatric syndromes consists of a search for a possible single disease that may have precipitated the symptom(s), and of a multiple risk factor assessment.57 This is done through a standardized comprehensive geriatric assessment, encompassing the somatic, psychiatric, social, and functional domain.28 Well known examples of geriatric syndromes are delirium, falls and incontinence.25 In sum, a geriatric syndrome results from the combination of a single or multiple specific diseases and / or from risk factors within the biopsychosocial domain.

Previously, gait speed has been advocated as a new ‘vital sign’ such as blood pressure and temperature in the diagnostic workup of a geriatric patient.29,30 This recommendation stems from studies that demonstrated associations between slowing of gait speed with failure of a wide array of specific organ systems, and with disability and mortality.14,31,32 Processing speed is regarded as a leading change of cognitive aging that is associated with cognitive defects in multiple other cognitive domains,
PCD, dementia and mortality (chapter six). In this thesis it is demonstrated that the associations of slowed gait speed and slowed processing speed with several adverse health outcomes are largely independent of each other. Processing speed explained only 10% of the associations between gait speed and falls, mortality and chronicity of depressive symptoms, while also gait speed explained only about 10% of the associations between processing speed and PCD and mortality. So, both slowing symptoms seem to operate independently from each other in predicting adverse health outcomes on both the somatic and psychiatric domain.

In other words, it is suggested that both slowing symptoms stem from different pathologies and summing them gives a better prediction of adverse health outcomes than only one of the two slowing symptoms. Slowing frequently occurs in old age, it is easy to recognize and it can be validly measured. As such, it can be seen as a geriatric syndrome that is easy to assess in daily practice that urges for a comprehensive geriatric assessment in case the slowing of gait or processing speed cannot be explained by an already diagnosed condition or conditions.

7.4 THE PATHOPHYSIOLOGY OF SLOWING IN LATE LIFE

Within the limitations of this epidemiological work, some considerations can be made with regard to possible underlying pathologies for slowing in old age. Apart from the association with specific diseases, slowing might be linked with adverse health outcomes through a number of underlying pathologies.

Slowed gait overlaps for a great part with the concept of sarcopenia, suggesting overlapping pathophysiological mechanisms. Sarcopenia is frequently seen in old age and it is defined as the loss of skeletal muscle mass and function with age. It is operationalized as slowed gait in combination with diminished handgrip strength and diminished muscle mass. Sarcopenia has gained a lot of attention from researchers and clinicians in geriatrics, as it is related to disability, morbidity and mortality in old age. Several mechanisms may be involved in sarcopenia, ranging from endocrine factors (decreased levels of steroid hormones, systemic inflammation), nutritional factors (inadequate amino acids intake or inappropriate caloric intake), and specific genes, to disuse (sedentary life style, immobilization). So, the association of slowed gait with adverse health outcomes might in part be the result of the same underlying mechanisms that are involved in sarcopenia.
Vascular disease is another mechanism that may explain the association between slowed processing speed and slowed gait with adverse health outcomes.\textsuperscript{39} One of the subtypes of vascular cognitive impairment includes subcortical ischemic vascular disease (SIVD). SIVD arises from small vessel disease and is characterised by extensive cerebral white matter lesions and lacunar infarcts in deep grey and white matter structures of the brain.\textsuperscript{40} It affects a number of cognitive domains, including processing speed when compared to normal controls,\textsuperscript{40} but another study also showed SIVD to be associated with impaired motor functions such as slowed gait speed.\textsuperscript{41} In both these studies, these effects were not explained by depressive symptoms. The authors conclude that depressive symptoms are linked with adverse health outcomes through another path than the slowing symptoms.\textsuperscript{40,41} These findings are congruent with the studies in chapter four and six, with regard to the association of the slowing symptoms with adverse health outcomes, where it is demonstrated that the associations are independent of depressive symptoms.

The independent and summing effects of both slowing symptoms suggest the presence of more than one explaining or underlying pathology, (chapter six) and this seems to contrast with a hypothesis of a common vascular pathology. Atherosclerosis itself however can be seen as a final common pathway of several underlying pathologies, and studies do suggest different risk factor profiles for intra- and extra-cerebral atherosclerosis.\textsuperscript{42} So, the concept of SIVD may well fit within the results of chapter six and may contribute to the association of motor and cognitive slowing with adverse health outcomes, which is not influenced by depressive symptoms.

In the above mentioned hypotheses primary (subclinical) diseases are suggested as an explanation for the associations of slowing with morbidity and mortality. Our results however may also fit in a hypothesis where slowing is interpreted as a form of secondary adaptation, a way of adapting to diminished capabilities that are associated with aging. In this hypothesis, slowing results from so called ‘noise’.\textsuperscript{43} Noise in this perspective is seen “as deviations from optimal behaviour, and therefore include suboptimal performance due to sensory, motor, conduction, or neural processing imperfections.”\textsuperscript{43} Slowing is interpreted as a strategy to survive with “noise”. Such an adaptation-to-noise-hypothesis can explain why in our studies underlying pathologies did not explain the associations of the slowing symptoms with adverse health outcomes.
7.5 SLOWING AND DEPRESSIVE SYMPTOMS, SUGGESTED USE IN DAILY PRACTICE

The findings of this community based study are relevant in daily practice for general practitioners and for physicians working with older people in an outpatient hospital setting. This thesis demonstrated that slowing is associated with a number of adverse health outcomes on the somatic (falls, mortality), and also on the neuro-psychiatric domain (cognitive decline, onset and course of depressive symptoms). When a patient demonstrates slowing of gait or slowing of thinking that is not understood from known diseases or disabilities, this slowing should prompt for a diagnostic workup, encompassing a comprehensive geriatric assessment.

From the results of this thesis, the following assessment is advised. If either one of the slowing symptoms (slowed gait or slowed processing speed) is perceived in a patient, the presence of the other symptom should be ascertained. After all, the two symptoms showed to have a moderate co-occurrence, and more importantly both slowing symptoms represent an independent risk for adverse health outcomes. The presence of the two slowing symptoms can be summed into a slowing sum score. This slowing sum score is a good predictor for PCD, falls and especially mortality. (chapter six)

Successively, the context of the slowing symptoms is relevant. In case slowing co-occurs in a patient with depressive symptoms, the slowing signals a subtype of depression with a more chronic course (chapter two and three). This subtype of late life depression may need a different therapy regimen. Yet, there is another reason to look for depressive symptoms in older people with slowing symptoms. In chapter six it has been demonstrated that the risk for adverse health outcomes is the same for people with and without depressive symptoms. Thus, in case older persons with a late life depression demonstrate psychomotor slowing, their risk for adverse health outcomes is possibly greater than for those without depressive symptoms, since the depressive symptoms themselves represent an independent risk to develop adverse health outcomes. See Figure 1 for a proposed diagnostic workup of patients presenting with a slowing symptom.
Summary and General Discussion

In chapter six it has been demonstrated that the risk for adverse health outcomes is the same for people with and without depressive symptoms. Thus, in case older persons with a late life depression demonstrate psychomotor slowing, their risk for adverse health outcomes is possibly greater than for those without depressive symptoms, since the depressive symptoms themselves represent an independent risk to develop adverse health outcomes.

Figure 1. Proposed diagnostic workup of patients presenting with a slowing symptom.

*: Slowed gait speed or slowed processing speed.
**: Resulting from the summing of both slowing symptoms

7.6 METHODOLOGICAL ISSUES

A personal clinical observation was that motor slowing and slowed thinking are common symptoms in later life that seem to cluster in specific patient groups. However, the outcome of our studies proved otherwise. The co-occurrence of both slowing symptoms in our studies is only moderate (chapter six). It is likely that this issue has to do with representativeness or external validity. As in all longitudinal population-based studies of older people, respondents in LASA are relative healthy, and thus clearly healthier than patients visiting geriatric outpatient clinics, but their impact on future morbidity seems to be independent of each other and not different from the more healthy older population. Yet, prevalence rates of depression and either slowing symptom are probably higher in the clinical geriatric population. As a result, it is likely that the demonstrated associations in this thesis may be even more pronounced in a geriatric population.

As a community based study focussing on consequences of physical, cognitive, emotional and social functioning in relation to aging, a number of clinical variables were not measured in as much detail as would have been possible in clinical studies (e.g. clinical data on risk factors for) vascular brain disease, longitudinal MRI’s). This may have increased the chance of residual confounding. Therefore, firm conclusions cannot be drawn with regard, for instance, to the causative influence of risk factors for cerebrovascular disease and several other possible underlying pathologies. On the other hand, thanks to the numbers of included respondents in LASA, it was possible to trace associations that may otherwise have remained unnoticed. As frequently with epidemiological research, the findings can be used as basis for further clinical research, where they have to be confirmed or rejected, and where underlying pathologies can be investigated.
In this thesis the presence of depression was not defined with a formal diagnosis; instead clinical relevant depressive symptoms were used. As a consequence the findings cannot limitess be extrapolated to patients with a DSM-classified depression such as Major Depressive Disorder (MDD). However also significant depressive symptoms have a great impact on health; people suffering from those have a higher conversion rate to MDD than people without depressive symptoms and also a higher risk for somatic comorbidities, disability and mortality.\textsuperscript{46-48} Also, a clinical dementia diagnosis based on formal criteria is unavailable in LASA. Instead, the presence of Persistent Cognitive Decline (PCD) was established, defined by using longitudinal data on MMSE, IQCode (see for details Chapter six). The concept of PCD has good face validity properties and moreover, in the latest Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) version \textsuperscript{49} the term dementia has been replaced with neurocognitive disorder, which comes close the criteria for PCD in LASA.

7.7 FUTURE RESEARCH

Slowing with or without depressive symptoms should prompt for a comprehensive geriatric assessment. This workup may uncover reversible conditions that are necessary to attend to. Whether this workup will help to shorten the duration of the depressive symptoms or even prevent the onset of new depressive symptoms is a subject for future research. Also, future research will have to demonstrate the content validity and clinical usefulness of slowing as a geriatric syndrome. A first step would be to define cut-off points differentiating pathological slowing from non-pathological slowing.

For gait speed several static cut-off points have been proposed, defining ‘seriously abnormal’, ‘mildly abnormal’, ‘normal’ and ‘superior’ gait speed, where a speed of less than 0.6 m/s is regarded as seriously abnormal,\textsuperscript{29} while others argue that 1.0 m/s already is a clinical significant cut-off point.\textsuperscript{50} Before slowed processing speed or a slowing sum score can be used in individual patient care, future research has to define cut-off points for these scores as well. Of note is that a gradual decline in speed may be part of the normal aging process, while in particular a change or an acceleration of slowing might be of greatest clinical significance. A longitudinally designed study did demonstrate that acceleration in the decline in gait speed and finger tapping in particular represents an early marker of Mild Cognitive Impairment (MCI).\textsuperscript{31} It thus might be useful to include longitudinal changes when distinguishing pathological from non-pathological slowing. With longitudinal designed cut-off points it may also be possible to account for inter individual differences or a personalized baseline speed profile. LASA, with its longitudinal design, offers a possibility to investigate these issues.
Processing speed is a cognitive measure of hierarchical importance for other cognitive domains and it declines with aging.\textsuperscript{20} In this thesis it is demonstrated that from a number of cognitive tests, especially processing speed had predictive abilities in predicting the course of depressive symptoms.\textsuperscript{\textit{chapter two}} Additionally, the combination of processing speed with gait speed has unique epidemiological characteristics as both markers are sensitive markers of declining health.\textsuperscript{14,34} Indeed, we demonstrated the combined potential with gait speed in this thesis with great predictive potential in clinical practice. However, although this test is simple, so far there are no generally accepted cut-off points, and it is not yet commonly used in standard geriatric practice. From our findings we think future research will have to develop these, as processing speed is a promising marker of health next to gait speed.

In this thesis treatment regimens were not investigated. A large body of research has been done questioning the benefits of exercise programs including walking on several outcome variables such as depression, adverse health outcomes and mortality. In younger adults exercise (involving walking, running, cycling, and/or swimming, at least 4 times a week, with a target heart rate of at least 55\% of the maximum heart rate) is moderately more effective than a control intervention for reducing symptoms of depression.\textsuperscript{52} Also in older people, physical exercise may be efficient in reducing clinical depression and depressive symptoms in the short-term.\textsuperscript{53,54} It has been demonstrated that training of processing speed may have beneficial effects on various cognitive functions.\textsuperscript{55} As both slowing symptoms may have different underlying pathologies, a combined training of gait speed and processing speed might be more effective than training either one of these domains. These training programs might prevent relapse and chronicity of depression and may also possibly reduce the speed of decline in patients with PCD. In 2006, such a combined training program was effective in reducing the prevalence of depressive symptoms in community dwelling residents aged 75–93 years until 5 years after the intervention.\textsuperscript{56} Future research will have to be done to further our knowledge on this kind of combined training programs that have the potential to reverse slowing and expand the reserve physical, cognitive and emotional capacity in old age.

Slowing is one of the main and charming characteristics of aging. This thesis however illustrates that slowing beholds clinical implications in older people and that it should be regarded as a marker of impeding decline of health in the care for older people, for those with and those without depressive symptoms.
REFERENCES


