Depressive symptoms, apathy, and adverse health outcomes in acutely hospitalized older patients

Research to get the ball rolling

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General discussion

Chapter 11
The main focus of the research presented in this thesis is on depressive symptoms and apathy as potential predictors of adverse health outcomes during the period of and after acute hospitalization among older adults. This is addressed in three ways: firstly, by assessing the prevalence of these syndromes compared with other geriatric syndromes; secondly, by analyzing the longitudinal effects of depressive symptoms and their associations with adverse health outcomes; thirdly, by analyzing specific depressive symptoms (e.g., feelings of hopelessness) and specific symptoms of apathy (e.g., loss of interest). This chapter will reflect on the primary findings of the research presented in this thesis. Following on from this, it will discuss methodological issues and the strengths of this research. Finally, it will discuss possible implications for clinical practice and will provide recommendations for further research.

**Reflection on main findings**

*Patient perspectives on post-hospital symptoms (Chapter 2)*

A qualitative study among 20 community-dwelling older persons who had recently returned home after acute hospitalization showed that patients reported difficulties in resuming their daily routines in the first two to three weeks post-discharge. They were mainly affected in their activities of daily living (ADL), leisure activities, and mobility. The majority of older persons attributed this negative impact on their daily routines to a limited number of geriatric conditions that included apathy, fatigue, unsteadiness while standing, and related fear of falling. Other symptoms that were frequently mentioned included muscle weakness, decreased appetite, and weight loss. Generally, patients appeared to be passively waiting to recover; this behavior goes against the current understanding that active recovery in the first weeks and months post-discharge is crucial to preventing persistent disability (Chapter 2).1

To denote the increased vulnerability in the post-discharge period, during which patients are at elevated risk of adverse outcomes, Krumholz2 introduced the term ‘post-hospital syndrome’ (PHS).2 Firstly it has been proposed that the reported geriatric symptoms in the qualitative study may reflect a manifestation of PHS, and may, according to the thinking of Krumholz,2 be the consequence of the adverse circumstances of hospitalization, such as malnutrition, bed-rest, and disturbed sleep during hospitalization.3-5 Three other possible etiologies in which patients are at elevated risk of adverse outcomes were described: sickness behavior, frailty, and being in the palliative phase. Firstly, it is proposed that patients may experience hospitalization-associated sickness behavior post-discharge, which is defined as a coordinated set of behavioral changes that occur in the case of infection, and are elicited by pro-inflammatory cytokines.6-8 Depressive symptoms, fatigue, apathy, psychomotor slowing, difficulty sleeping, and decreased appetite are characteristic symptoms of sickness behavior, and these corresponded with symptoms experienced by older persons who had been acutely hospitalized and discharged home.9 There are also two non-mutually exclusive explanations for the experienced symptoms. For example, it is possible that the effects of acute hospitalization can become manifest in the development or worsening of frailty symptoms, given that at least three symptoms of the frailty criteria were frequently reported by participants, i.e., weight loss, perceived weakness, and fatigue,10 which coincidentally also overlap with diagnostic
symptoms of depression. In addition, many patients felt unsteady while standing and were affected in their mobility, which could indicate two remaining frailty criteria (i.e., slow walking speed and low physical activity). Frail older persons are at great risk for acute hospitalization, and a characteristic feature of frailty is the reduced ability to recover homeostasis and functioning after stressors such as acute medical illness and hospital admission. Finally, the constellation of syndromes may be a reflection of the palliative phase older persons are in. Most reported symptoms (e.g., fatigue, weight loss, loss of appetite, and unsteadiness while standing) are symptoms that patients report during the palliative phase. Acute hospitalizations are frequent in the final year of life, which in turn plays a role in deterioration during this final phase (Chapter 2).

Geriatric syndromes during and after acute hospitalization (Chapters 3 and 4)

Most previous studies focusing on functional decline among acutely hospitalized older patients have utilized relatively long follow-up intervals (e.g., from acute hospital admission up to three months or more). Thus, information is lacking on syndromes and outcomes that are present during the first months post-discharge, which are thought to be critical to recovery. Following up on the qualitative results, a quantitative longitudinal study was designed and conducted (Chapter 3) that involved geriatric syndromes assessment in the pre- and post-discharge period, also intending to acquire data that could help early identification of patients at risk of further functional deterioration. This study was denoted as the hospitalization-associated disability and impact on daily life (Hospital-ADL) study. The main focus of this study was to unravel underlying mechanisms behind hospitalization-associated disability (HAD), which is defined as the loss of ability to perform one or more of the basic ADL compared to the patient’s abilities two weeks prior to acute hospitalization. HAD is the leading cause of loss of independence in ADL among older individuals and it is a complex and highly dynamic process with possible recurrent disability episodes in older patients. The first month after acute hospitalization has been identified as a crucial period for recovery, after which disabilities have a high risk of becoming permanent and patients with additional disabilities are at high risk of other adverse outcomes within three months post-discharge, including readmission and mortality. The main aim of this thesis was the assessment of geriatric syndromes, in particular, depressive symptoms and apathy, and to determine their predictive utility for identifying patients at risk of HAD. In this study, from among 1,024 acutely hospitalized patients, involving six hospitals in the Netherlands, a total of 401 agreed to participate. This study was run between October 2015 and February 2018. This cohort study provides the data for all subsequent chapters.

The aim of Chapter 4 was investigating the prevalence and course of a broad spectrum of geriatric syndromes among acutely hospitalized older patients. In addition, this study determined the probability of retaining geriatric syndromes in the post-discharge period that were also present at admission. Geriatric syndromes included were depressive symptoms (including apathy), fatigue, cognitive impairment, pain, incontinence, malnutrition, dizziness, fall risk, functional impairment, mobility impairment, and fear of falling. Results showed that at admission geriatric syndromes were highly prevalent with a
median number of geriatric syndromes of five per patient. Fatigue, functional impairment, apathy, mobility impairment, and fear of falling showed the highest prevalence. Although results showed that the number of syndromes decreased post-discharge, prevalence rates of geriatric syndromes remained high post-hospitalization, with a median number of four and three syndromes being present at one and three months, respectively, post-discharge. In addition, when a geriatric syndrome was present at admission, this syndrome was likely to remain for the first three months post-discharge. The non-transient nature of the geriatric syndromes was particularly prominent for depressive symptoms, mobility impairment, incontinence, cognitive impairment, functional impairment, and fear of falling.

As aforementioned, it was proposed that acutely hospitalized older patients may be vulnerable to a PHS. However, the finding that a broad spectrum of geriatric syndromes was already highly prevalent at admission, may suggest that these syndromes were already present before acute hospital admission. Therefore, it seems plausible that patients were already frail before admission to the hospital, especially because frequent features of frailty (i.e., fatigue, mobility impairment, and malnutrition) were also reported by the current Hospital-ADL study population within 48 hours after admission. In addition, there is ample evidence that frailty is an important predictor of hospitalization. The finding that patients are likely to retain geriatric syndromes during acute hospitalization and post-discharge (Chapter 4), could be explained by a hospital-related allostatic overload. Allostasis refers to a system functioning with normal stress-response parameters to achieve stability. For example, the body responds to almost any challenge by releasing neuroendocrine mediators that help to physically and mentally cope with the situation. However, chronic elevation of these same chemical mediators may produce chronic “wear and tear” and can result in adverse health outcomes, denoted as “allostatic load or overload”. Acutely hospitalized older patients are routinely and repetitively exposed to a wide variety of environmental stressors such as the aforementioned sleep disruption, mobility limitations, unfamiliar environments, unknown roommate, and loud noise, which gradually impair adaptive responding, rendering patients more vulnerable to adverse health outcomes. Because allostatic load described similarities with frailty (i.e., impaired ability to recover homeostasis and functioning after stressors) it is important to note that different concepts can be applied in parallel to capture the same phenomena.

The course of depressive symptoms and their predictive value for adverse health outcomes (Chapters 5 and 6)
The first chapters confirmed that geriatric syndromes overall tend to be stable, but some highly prevalent syndromes (such as fatigue) slightly decrease post-discharge, and some less prevalent syndromes (e.g., depressive symptoms) appeared to be persisting post-discharge (Chapters 3 and 4). Therefore, Chapter 5 aimed to identify distinct trajectories of depressive symptoms from acute admission, up to three months post-discharge, and whether these distinct trajectories were associated with adverse short-term outcomes such as HAD, falls, unplanned readmissions, and mortality. The Geriatric Depression Scale-15 (GDS-15) was used to measure depression; this instrument is specifically
developed for a geriatric population, widely used in acute hospital settings, and predominantly includes cognitive-affective symptoms to rate probable depression, purposely omitting somatic symptoms. This latter aspect is because these somatic depressive symptoms may be confounded by an acute medical illness or features of the aging process, i.e., somatic diseases among older adults may be mistaken for somatic symptoms of depression, which complicates interpretation of a symptom score in terms of the probable presence of depression. Group-based trajectory modeling (GBTM) identified three distinct cognitive-affective depressive symptom trajectories among acutely hospitalized older adults, assessed from acute admission up to three months post-discharge: minimal symptoms (63.6%), mild and persistent symptoms (25.4%), and severe and persistent symptoms (11.0%). Hence, nearly 40% of the patients experienced persistent mild to severe depressive symptoms. Nearly 50 and 90% of the patients with, respectively, mild and severe persistent symptoms have a score of six or above (cut-off value) on the GDS-15 at admission. Additionally, unadjusted results showed that these two trajectories were associated with a substantially higher risk of functional decline, falls, and mortality. Furthermore, the two trajectories with elevated depressive symptoms can be distinguished from the minimal depressive symptoms' trajectory by several baseline variables, such as not being married, being admitted to the Department of Geriatrics, having more medical comorbidities, being more cognitively impaired, being malnourished, and having higher anxiety (Chapter 5). Notably absent, was a 'recovering trajectory', which might have been expected if elevated depressive symptoms were a merely transient-reactive response to hospitalization. This further emphasizes the need for acute care hospitals to develop discharge or screening procedures for targeting depressive symptoms.

Subsequently, in Chapter 6, the course of depressive symptoms was investigated over a longer follow-up period (i.e., up to one year post-discharge) and their longitudinal association with both basic and instrumental activities of daily living (ADL and IADL) was determined. Results showed that over a year for both cognitive-affective depressive symptoms, ADL and IADL function improved slightly. Consistent with previous longitudinal research, this study found the course of depressive symptoms to be associated with increased dependencies in both ADL and IADL. However, unlike previous research, this study disentangled the between- and within-subject components, which enables us to examine whether changes in depressive symptoms are associated with changes in ADL and IADL functioning, by using a hybrid model. This distinction is relevant because in order for a variable to function as an intervention target for another variable, the variables should not only be associated at the group level, but changes in the variables should also be associated at the individual level. In addition, this study describes the rate ratios (RR) instead of using unstandardized beta regression coefficients, which makes it possible to describe the percentage change in ADL and IADL associated with a one-point increase in depressive symptoms. This study found that if depressive symptoms increase by one unit, ADL independence decreases by 9% and IADL independence decreases by 6%, equivalent to an increase of .63 and .54 on the Katz-ADL and IADL scales (i.e., more dependencies in ADL and IADL), which comprises a range of 0–6 points. Furthermore, both the between- and within-person effects of depressive
symptoms were significantly associated with the course of ADL and IADL function, which withstood adjustment for a range of confounding variables. If depressive symptoms between subjects increase by one unit, ADL independence decreases by 15% and IADL independence decreases by 13%, equivalent to a decrease of 1.05 and 1.17 on the Katz-ADL and IADL scales, respectively. If depressive symptoms within subjects increase by one unit, ADL independence decreases by 6% and IADL independence decreases by 5%, equivalent to a decrease of .42 and .45 on the Katz-ADL and IADL scales, respectively. So, depressive symptoms and ADL and IADL functioning are not only linked at the group level (i.e., between-subjects) but also at the individual level (i.e., within-subjects). These significant findings support the idea that to study the relationship between depressive symptoms and change in functional abilities longitudinal analyses are preferable, rather than only a cross-sectional study. The described substantial changes in ADL and IADL scores mostly lie above or just below the previously estimated .50 minimally important change (MIC) for both ADL and IADL scales, implying clinically relevant changes.

However, it is important to note that much previous research, like Chapters 5 and 6, reported the association between depressive symptoms and functional decline by using instruments that include several apathy items and by not making this distinction. The previously widely reported association between depressive symptoms and functional decline may be confounded by symptoms of apathy and these symptoms may contribute to adverse health outcomes. Therefore, Chapter 6 provided supplementary results of this distinction, finding that both geriatric syndromes (i.e., depressive symptoms and apathy) were significantly associated with changes in ADL and IADL over time. The RR was lower for symptoms of apathy in comparison with depressive symptoms, which means greater changes in ADL and IADL scales (i.e., more dependencies in ADL and IADL) among patients with symptoms of apathy.

Specific symptoms of depression and apathy and their predictive value for adverse health outcomes (Chapters 7 and 8)

Elaborating on previous findings, Chapters 7 and 8 made the distinction between depressive symptoms and apathy and therefore being able to investigate the role of these syndromes with adverse health outcomes. Chapter 7, therefore, aimed to examine the prevalence of specific depressive symptoms during acute hospitalization among older patients, as assessed by the GDS-15. In addition, this study investigated the value of both the overall sum-score and specific depressive symptoms for predicting mortality during the three months post-discharge. In line with prior research, higher levels of depressive symptoms predicted mortality in these patients. Item-analyses revealed that the three most frequently reported cognitive-affective symptoms during hospitalization pertained to the construct of apathy (i.e., loss of activities and interests, loss of energy, and a preference to stay at home). Another novel finding was that feelings of hopelessness were a strong predictor of all-cause mortality, even after adjustment for potential confounders such as somatic symptoms and disease severity. Specifically, between 40 and 45% of patients who reported feeling hopeless about their situation during acute hospitalization died between admission and three months post-discharge (Chapter 7).
In light of the high prevalence of symptoms of apathy during and after acute hospitalization (reported in Chapters 2, 4, and 7), Chapter 8 investigated the prevalence of persistent symptoms of apathy among older patients as a predictor of loss in ADL. Previous research has shown that persistent symptoms of apathy were predicting a loss of autonomy in activities of daily living among older patients with Alzheimer’s disease. However, currently missing are studies investigating persistent symptoms of apathy in a more general older patient population after an acute hospitalization. Persistent symptoms of apathy were defined as reporting symptoms of apathy in the four weeks post-discharge. Apathy was measured with the GDS-3A, regarded as a separate three item subscale of the GDS-15. This study found that nearly 30% of the older patients experienced persistent symptoms of apathy in the first critical month post-discharge. At admission, these patients were more likely to have been admitted to the Department of Geriatrics and reported more functional limitations, more (cognitive-affective) depressive symptoms, more symptoms of apathy, more malnourishment, and higher levels of pain within 48 hours after acute admission in comparison with patients with non-persistent symptoms of apathy. This may aid the identification of patients at high risk of developing HAD. With regard to the last aim, the results showed that patients with persistent symptoms of apathy, in particular, those reporting "a preference to stay at home" had a five-times higher risk of loss of ADL (p < .001). Thus, we can identify apathy as a robust independent predictor of HAD after acute hospitalization. It may, therefore, be worthwhile to further consider apathy symptoms as a possible routine screening item among this patient population and a target for intervention (Chapter 8).

Based on the findings of Chapters 7 and 8, it appears that symptoms of apathy and feelings of hopelessness may be linked with frailty or are a reflection of the palliative phase. Most research on frailty has been focused on biological mechanisms, rather than on the contribution of mental conditions to the onset and progression of frailty. Hale et al developed a schematic model summarizing potential factors involved in the onset of frailty, including biological, resilience, social and community networks, socio-economic and living conditions, and individual factors. Evidence indicates that symptoms of apathy are associated with frailty among non-demented, community-dwelling older adults. Future research may focus on the expansion of this model to explore the extent to which feelings of hopelessness and apathy are also potential factors of frailty among acutely hospitalized older patients. Finally, because feelings of hopelessness were associated with mortality, patients possibly feel their downfall during acute admission.

General self-efficacy, motivational factors, and goal-setting (Chapter 9 and 10)

Research has shown that general self-efficacy (GSE) is associated with functional disabilities in ADL in older adults. Following up on the results that depressive symptoms are associated with impaired functional performance outcomes over time, Chapter 9 aimed to determine the mediational role of common geriatric symptoms (i.e., depressive symptoms, apathy, and fatigue), by focusing on a motivational aspect in the relationship between GSE and physical performance outcomes. Structural equation modeling (SEM) was used to analyze these relationships. Results showed that lower GSE at hospitalization was associated
with a worse course of subjective (i.e., ADL and IADL) and objective physical performance outcomes (i.e., Short Physical Performance Battery (SPPB)). However, when motivational factors (i.e., depressive symptoms, apathy, and fatigue) were taken into account, motivational factors, and no longer GSE became significantly associated with both IADL and SPPB. Motivational factors also (partially) mediated the relationship between GSE and ADL. A possible explanation for the partial mediation finding could be that motivation may play a smaller role in many of the basic ADL that recur at routine intervals compared with more complex activities such as IADL. With the repetition of behavior in stable contexts, actions become more automatic in the sense that deliberation about actions is superfluous. Although previous research established that self-efficacy beliefs are associated with worse functional outcomes, the current findings indicate that for the population studied here, motivational factors (and not GSE per se) may account for this relationship, particularly in the case of more complex physical activities (Chapter 9). Taken together, this suggests that GSE is relevant to being physically active but not sufficient to becoming more physically active in acutely hospitalized older patients; motivation is important to improve both subjective and objective performance among this population.

Within the field of geriatric rehabilitation (e.g., recovery in ADL), motivation is typically viewed as an important concept, and goals and goal-setting are fundamental components. Therefore, Chapter 10 aimed to review the psychometric properties of goal-setting instruments that are used within geriatric rehabilitation. Of the 11 studies that were included, seven studies assessed the Goal-Attainment Scaling (GAS), two evaluated the Canadian Occupational Performance Measure (COPM) and one the Self-Identified Goals Assessment (SIGA), which is based on the COPM. Finally, one study evaluated a core set of the International Classification of Functioning, Disability and Health (ICF) framework. Overall, there has been little research conducted in the area of goal-setting in geriatric rehabilitation. The existing studies support GAS as a goal-setting instrument, given the high concurrent, content, and predictive validity, and inter-rater reliability. Moreover, the responsiveness appears to be excellent. However, future research is required to evaluate GAS as a goal-setting instrument and routine outcome measurement in different health care settings. Before the COPM (or SIGA) can be recommended as a goal-setting instrument, its psychometric properties require further research. Taken together, patient goals set with GAS can be used as an additional outcome measure, rather than as replacement for standardized measures, within geriatric rehabilitation or transitional rehabilitation interventions.

Based on the findings of Chapter 9, it seems to be important that goal-setting may shift to focus on improving motivational factors such as depressive symptoms and apathy, taking into account two previously described neurobiological motivation systems: a behavioral activation system that is characterized by sensitivity for reward and a behavioral inhibition system that is characterized by threat. Previous research described depression as being marked by low levels of behavioral activation. These two motivation systems are linked to the type of goals that are set: approach- or avoidance-oriented goals. Approach goals are represented by goals that a person is aiming for and avoidance goals by staying away from an undesirable target. It seems conceivable that older
people with depressive symptoms will set low approach-oriented goals. Dickson et al.\textsuperscript{61} suggested that conditional goal-setting might hamper successful goal achievement. Conditional goal-setting refers to “the tendency to view high-order goal attainment, such as life satisfaction, fulfillment, and self-worth, as entirely dependent on the achievement of lower-order goals”.\textsuperscript{61} People with depressive symptoms (i.e., conditional goal-setters), especially patients with a feeling of hopelessness about their future,\textsuperscript{64} set goals in an unhealthy way: they believe that happiness can only be achieved by the attainment of specific goals.\textsuperscript{63}

**Methodological considerations**

*Generalizability: Qualitative study design*

Chapter 2 describes the results of a qualitative study in which 20 community-dwelling older adults were included. Although the small sample size might have limited generalizability, the researchers continued interviewing until saturation occurred. The finding that patients experienced different geriatric syndromes that they linked to adverse health outcomes post-discharge served as the basis for the start of the Hospital-ADL study. In fact, to our knowledge, this was the first qualitative study that focused on patient experiences regarding recovery during the post-discharge period.

*Generalizability: Hospital-ADL study*

This thesis includes primarily data from the longitudinal Hospital-ADL study (Chapters 4–9). There are several limitations regarding the generalizability of the Hospital-ADL study. Firstly, as with all longitudinal studies, there was a lack of follow-up, which resulted in complete assessments being more likely to be available for the relatively healthy patients, thereby introducing a bias. Therefore, the outcomes in the aforementioned chapters may have been underestimated. Secondly, the observational nature of the Hospital-ADL study limits the ability to draw causal conclusions between geriatric syndromes and adverse health outcomes. Thirdly, the Hospital-ADL study did not include delirious or severely cognitively impaired patients. One major reason for this exclusion was the fact that the validity of the Geriatric Depression Scale (GDS) significantly decreases in patients with a Mini-Mental State Examination (MMSE) score equal to or less than 15.\textsuperscript{65,66} The prevalence of geriatric syndromes described in this thesis may therefore reflect an underestimation of actual prevalence, since geriatric syndromes are more commonly found in patients with delirium.\textsuperscript{67} Fourthly, during the Hospital-ADL study, it was not possible to include data on the history of depression, treatment of depression, or anti-depressant use, as this information was often not part of hospital records. As a result, it was impossible to control for the potential effect of pre-existing depression and antidepressant medication on geriatric syndromes. Furthermore, because depression was not determined by clinical interview (e.g., DSM5, ICD-10), it was not possible to determine what proportion met the formal criteria for major depression. However, whether some patients would have received a clinical diagnosis seemed less relevant to the objectives of this thesis, as the focus in the chapters is on the severity of symptomatology, and not on clinical diagnosis per se (Chapters 4–9). Finally, because older individuals in comparison with younger adults are less likely to endorse cognitive-affective depressive symptoms,\textsuperscript{68} such
as feelings of hopelessness, the observed results from Chapter 7 may have been underestimated.

**Strengths**
The research in this thesis has several strengths. Firstly, the design of the longitudinal Hospital-ADL study is characterized by frequent measurements during acute hospitalization, and in the critical period for recovery\(^1\) post-discharge. This longitudinal design is particularly useful for evaluating relationships between risk factors and the development of adverse health outcomes, which allows analyzing change over time for a group or for individuals. To our knowledge, this is the first study that has addressed the dynamic nature of depressive symptoms during and after acute hospitalization by high temporal resolution, which may provide useful information for acute hospital settings. Another strength was the extensive assessment that was conducted at all-time points, which covered medical and demographical data, cognitive functioning, behavioral and psychological functioning (e.g., fear of falling, anxiety, apathy, depressive symptoms, and GSE), ADL/physical functioning, somatic symptoms (e.g., pain, fatigue, body mass index, weight loss, and loss of appetite), health care utilization, physical performance test (e.g., handgrip strength, agility, activity trackers), and blood parameters. Thirdly, depressive symptoms and apathy were measured using the GDS-15, which has been specifically developed for older adults and does not include items on somatic symptoms that may be confounded by symptoms of acute medical illness or the aging process.\(^69,70\) The latter may result in an overestimation of depressive symptoms. In attempting to differentiate between depression and medical complaints, existing research suggests that using questionnaires that focus less on the somatic aspects of depression, and more on the cognitive-affective depressive symptoms, may highlight the best indicators of depression and symptom change in older adults.\(^34,69\) Finally, geriatric syndromes, depressive symptoms, and apathy were analyzed by using sophisticated data analyses (e.g., GBTM, hybrid models, and SEM), which provided acute hospital care settings guidance for the management of these symptoms.

**Implications for clinical practice**

*Geriatric syndromes*

Traditionally, the hospital setting is mainly focused on the management of an acute medical illness and ensuring the earliest discharge of patients,\(^71\) resulting in geriatric syndromes that may be overlooked and remain after hospitalization. In these cases the syndromes are linked to adverse health outcomes after acute hospitalization, including mortality and the loss of ability to perform one or more basic ADL.\(^16,72\) The first part of this thesis has shown that a high prevalence of geriatric syndromes are present in the first month after acute hospitalization. These syndromes have a negative impact on resuming daily routines, because older patients appear to passively wait for recovery instead of taking a more active approach in this critical first month post-discharge seems to be a disturbing problem (Chapter 2). Previous research has shown that older persons may not recognize all geriatric syndromes as problematic.\(^73\) It is conceivable that this misinterpretation could explain why patients were observed to passively
wait to recover. Furthermore, the finding that geriatric syndromes seem to be already highly prevalent within 48 hours after admission and likely to remain post-discharge (Chapter 4), suggests that vulnerabilities in patients may already be present before acute hospital admission. This would suggest the presence of a frailty syndrome rather than a post-hospital syndrome. Therefore, adequate follow-up care about the presence of geriatric syndromes is crucial to reduce or prevent adverse health outcomes such as HAD and mortality. It is conceivable that information on the presence of geriatric syndromes post-discharge may help older adults to adequately interpret these syndromes and help them to become more active. However, as shown in this thesis, a large proportion of the acutely hospitalized older patients feel apathetic (Chapter 2, 4, and 7) and do not feel like doing anything (Chapter 2), which is predictive for HAD within three months post-discharge (Chapter 8). Chapter 9 shows that it seems important to improve, in particular, motivational factors (e.g., depressive symptoms and apathy) (Chapters 5, 6, 8, and 9) in the first month post-discharge (Chapter 8), to encourage older adults to become more physically active during and after acute hospitalization, thereby reducing or preventing HAD.

**Depressive symptoms and apathy**

Given the high prevalence and upshot of depressive symptoms and apathy in acutely hospitalized older patients, it is arguably relevant that health care professionals pay attention to these syndromes. Firstly, they should be aware that depressive symptoms often do not improve spontaneously after acute hospitalization (Chapter 5) and that they are associated with adverse health outcomes such as functional decline, falls, and mortality (Chapters 5 and 6). Although there is ample evidence that depressive symptoms are highly prevalent among inpatients, these symptoms are often undiagnosed and untreated. This appears to be a crucial issue because a large proportion of the inpatients develop clinically depressive disorders during non-psychiatric hospitalizations. Previous research found that non-psychiatrist physicians overlooked a large proportion of depressive symptoms that were recorded by well-trained psychiatrists. A plausible explanation for the under-recognition of depressive symptoms is the large overlap with other symptoms or disorders. There is a high overlap between dementia and depression, dementia and apathy, somatic symptoms and depression, apathy and depression, and older adults under-recognizing their depressive symptoms, which may create complexity for recognizing depressive symptoms among health care professionals. However, today, a depression status is mostly determined by summarizing a range of symptoms until a pre-determined cut-off value is met. This approach belies the true complexity of depression as a heterogeneous syndrome whereby different patients may display distinct symptom constellations and show different associations with adverse health outcomes (Chapters 7 and 8). Therefore, this thesis considered the complex psychopathology of depressive symptoms and apathy among older persons by using a dimensional approach instead of using a categorical approach. A categorical approach results in labeling each person as having or not having a disorder and a dimensional approach results in labeling each individual with an ordinal score, with higher scores indicating a stronger likelihood of having a disorder. The latter has the
advantage in that it deals with the problem of applying diagnostic criteria or pre-determined cut-offs to define disorders. Based on our findings and previous literature, it appears crucial to address depressive symptoms as part of health care policies, and there is a need for the improvement of screening instruments and intervention options for targeting depressive symptoms during acute hospitalization. Secondly, the finding that persistent symptoms of apathy were associated with HAD, means that measuring symptoms of apathy longitudinally is more clinically informative than cross-sectional. Potentially, the focus should shift to identifying those patients who do not recover from apathy in the first month post-discharge, rather than on all patients showing apathetic symptoms during acute hospitalization or at discharge. Although Chapter 8 found that symptoms of apathy during acute admission were already predictive for HAD, this study also found that if the symptoms of apathy improve in the first month post-discharge it was no longer associated with HAD within three months post-discharge. These outcomes indicate that improvement in geriatric syndromes in the first month after acute hospitalization seems to be crucial for reducing or preventing HAD (Chapter 8). Thirdly, item-level analyses of depressive symptoms and apathy indicated that feelings of hopelessness about their situation and apathy (i.e., GDS-3A item preference for staying at home rather than going out) were associated with adverse health outcomes after acute hospitalization, including mortality and HAD (Chapters 7 and 8). However, nowadays, the administration of the GDS is not a standard part of the comprehensive geriatric assessment (CGA) in the Netherlands,93 which is defined as a “multidisciplinary diagnostic process intended to determine a frail older person’s medical, psychosocial, and functional capabilities and limitations in order to develop an overall plan for treatment and long-term follow-up”.94 Professionals need to be aware of the association with adverse health outcomes of the two aforementioned GDS-15 items (i.e., items 9 and 14). Therefore, they may be useful screening questions, which can be added to the CGA to determine frail, older individuals.

Treatment of depressive symptoms and apathy
The implementation of CGA among older people in an in-hospital setting has proven to be effective in that these patients were more likely to survive and return home and less likely to be admitted to a nursing home within one year post-discharge.95 Furthermore, based on the findings that depressive symptoms and symptoms of apathy are highly prevalent during acute admission implies that older patients may need treatment for their symptoms during and after acute hospitalization. However, what is important to note is that research has shown that depressive symptoms should be treated differently from apathy in which antidepressants should be used with caution in depressed persons.96 For example, selective serotonin reuptake inhibitors (SSRIs) help with the improvement of depressive symptoms, but it may worsen symptoms of apathy.97 Dopaminergic agents have been reported to be useful in patients with apathy. However, there is no current consensus about the treatment of apathy, but this should be selected according to the underlying etiology of the disease for ameliorating apathy.98 For example, dopamine agonists seem to be effective in patients with Parkinson’s disease, atypical antipsychotics in schizophrenia work well to treat negative symptoms, and cholinesterase inhibitors are beneficial in patients with Alzheimer’s disease.
and other dementia. Cognitive behavioral therapy (CBT) or behavioral activation (BA), on the other hand, are evidence-based non-pharmacological approaches to treat depressive symptoms. However, given the focus on cost reductions in health care settings, there is limited time for the provision and coordination of these interventions during hospitalization. Therefore, it should be thought of transitional care interventions, which refers to the coordination and continuity of health care during a transition from a hospital setting to another setting or home. Research has shown that transitional care interventions, compared to general care, result in significantly better outcomes as related to re-admissions and mortality rates post-discharge among older adults. To also prevent functional decline or to stimulate physical activity post-discharge, transitional care interventions seem crucial, including a CGA, home rehabilitation, and individual treatment goals. The positive effects of patient-centered goal-setting are widely recognized in geriatric rehabilitation centers, in which goals are mostly related to regaining independency in ADL. However, it might be too ambitious to implement a comprehensive goal-setting process in the context of acute care, possibly further complicated by a discrepancy between the geriatric patients’ and the professionals’ views regarding recovery goals. Patients wish to regain independence in ADL whereas health care professionals focus on discharge-related goals. Therefore, professionals should make a distinction between goals that are important to achieve during acute hospitalization and in the post-discharge period during home rehabilitation. Moreover, given the high prevalence of apathetic symptoms among acutely hospitalized older patients, which could be an explanation for the high levels of physical inactivity during acute hospitalization, it is conceivable that it may be difficult for older patients to achieve goals post-discharge. Therefore, it seems crucial that professionals set goals that are easy to accomplish, and, among patients with depressive symptoms and feelings of hopelessness, it appears crucial to encourage to thinking of goals as a process rather than outcome. Furthermore, professionals need to be aware of the levels of conditional goal-setting within individuals because it is associated with depressive symptoms and feelings of hopelessness and persons with higher levels are more inclined to believe that well-being depends on achieving goals. These patients will continue to pursue unattainable goals, which may result in (even) more depressive symptoms and symptoms of apathy. In other words, professionals may pay attention to a home rehabilitation approach addressing older patients’ attainable goals post-discharge that are adjusted to the individual’s activities and daily needs. Home rehabilitation appears to be a good option within this population because recovery, to a large extent, takes place at home and they experience difficulties in resuming their daily routine. Patient-centered goals may be set by using an instrument such as Goal Attainment Scaling (GAS), given the excellent responsiveness and high concurrent, content, predictive validity, and inter-rater reliability. GAS can be used as an additional outcome measure next to standardized instruments, such as the Katz-ADL index, because they detect clinically important changes that would be overlooked with just standardized instruments (Chapter 10). It is important to note that, to help older patients to accomplish their goals, home rehabilitation interventions should also be focused on behavioral activation and exercises to improve mobility. Therefore, thought
should also be given to the use of sensor monitoring in combination with the coaching of CBT principles by occupational therapists, of which goal-setting is a component, to improve ADL and physical activities back at home.113, 114

**Implications for education**

In this thesis we observed that symptoms of apathy are frequently reported among acutely hospitalized older adults (Chapters 2, 4, and 7) and depressive symptoms are highly persistent and persistent after acute hospitalization (Chapter 5) and that these syndromes were associated with adverse health outcomes (Chapters 5–9). To achieve a smooth and effective discharge, which is associated with higher satisfaction and fewer readmissions among older adults, professionals need to become competent in effective discharge planning. Studies have demonstrated the effectiveness of crucial elements of discharge planning to improve patient empowerment and expectation management: adequate communication, patient participation in all communication, efficient coordination to reduce stress, and patient education.114, 115 Therefore medical students should be encouraged to become competent in discharge planning before starting as physicians. Furthermore, clinical training could be offered to physicians and health care professionals not accustomed to assessing psychiatric disorders in order to better detect the presence of depressive symptoms and apathy to reduce or prevent poor performance outcomes. Thirdly, professionals need to be more aware of the low physical activity among acutely hospitalized older patients during hospitalization,108, 109 which can be a consequence of symptoms of apathy, resulting in a passive attitude towards post-discharge recovery. Education by health care professionals for patients and caregivers to discuss the importance of behavioral activation during and after acute hospitalization as well as the relationship with activity engagement in older individuals may be helpful.115

**Future research**

This thesis offers several future research perspectives to the field of geriatric syndromes, particularly with regard to research on depressive symptoms and apathy. Firstly, future studies may also shift to include possible biological mediators of elevated depressive symptomatology and apathy. Differentiating apathy from depression within the context of inflammation is important since research has found a differential effect of inflammation on apathetic and depressive symptoms.118 Elaborating on the results of this thesis describing the different predictive values of depressive symptoms and apathy for adverse health outcomes (Chapters 7 and 8), suggest also different underlying causes and maintaining factors, and therefore may display different associations with inflammatory markers. A more thorough examination of the association between inflammatory markers, apathetic and depressive symptoms is especially interesting in older persons considering the effect of aging on the immune system.8, 119-122 The aging process appears to be related to persistent changes in the immune system, specifically to a pro-inflammatory state.120, 122, 123 In line with the above-mentioned, it would be relevant if future research can shift to focus on the different etiologies of adverse health outcomes among acutely hospitalized older patients. It seems conceivable that frail older patients with symptoms of
apathy, patients with sickness behavior, patients with an allostatic overload, or patients who are in the final phase of their lives all need a different approach. Secondly, the results found that patients with depressive symptoms and apathy also significantly experience difficulties in presuming instrumental activities of daily living (IADL) after acute hospitalization (Chapters 2, 6 and 9), which may suggest that a broader view of HAD is needed, which now is solely focused on the loss of basic activities of daily living.\textsuperscript{17} Thirdly, it would be helpful if future research may focus on a standardized method of documenting non-psychiatrists’ recognition of depression and symptoms of apathy to improve their accuracy in recognizing of these symptoms among inpatients. In line with this, it would be helpful if future research aims to identify both effective pharmacological and non-pharmacological apathy specific treatments. Fourthly, more research is, for example, warranted to understand the complex associations between specific depressive symptoms and adverse health outcomes during and after acute hospitalization among older adults. A network analysis model can be used to assess how specific symptoms of depression relate to adverse health outcomes.\textsuperscript{124} Fifthly, in this thesis, feelings of hopelessness were measured using two items of the Dutch version of the GDS-15, one of which has a more trait-like focus, and examines whether patients often feel hopeless, whereas the second item examines patients who feel hopeless about their situation (state hopelessness).\textsuperscript{125} Only the latter was a significant predictor for mortality within three months post-discharge (Chapter 7). This suggests that research is needed on the potential differential impact of state and trait hopelessness and interventions targeting hopelessness. Furthermore, previous research has found that feelings of hopelessness about the future are a crucial component of suicidal behavior.\textsuperscript{126} This thesis has no data on cause of death as it was not the focus of the Hospital-ADL. Future research could usefully look to such data, including suicide, to further illuminate the mechanisms by which hopelessness is related to mortality. Finally, future studies may focus on examining the effectiveness of home rehabilitation on goal attainment among older persons after acute hospitalization. Although there is little evidence that higher conditional goal-setting is related to depression\textsuperscript{63} and hopelessness,\textsuperscript{64} no research has yet been investigated these in association with symptoms of apathy.

**Final conclusion**

The findings presented in this thesis provide evidence that depressive symptoms and apathy are associated with adverse health outcomes during and after acute hospitalization among older patients, such as HAD and mortality. Given the high prevalence and upshot of depressive symptoms and apathy in acutely hospitalized older patients at admission and after acute hospitalization, it is arguably relevant that health care professionals need to be aware of these syndromes and also better recognize them next to the management of acute medical illness. Therefore, education for professionals about depressive symptoms and apathy in older adults seems to be crucial to recognizing these symptoms better among this population. To reduce or prevent poor outcomes, it may be useful if two GDS-15 items (i.e., feelings of hopelessness about their situation and preferring to stay at home rather than going out) will be included as screening questions in the CGA for identifying patients who have a greater risk
to be in the final phase of their lives or who are at greater risk of developing HAD. Furthermore, and in line with previous research, the first month(s) after acute hospitalization seems to be crucial for recovery, and, therefore, implementation of a CGA among older persons and transitional care interventions seems to be crucial. Future studies could investigate the effects of patient-centered goal-setting during and post-discharge (i.e., home rehabilitation), during which it is important to set achievable goals to achieve satisfaction and motivation in this vulnerable population. Even more essential might be that future studies may shift to pay more attention to the possible etiologies (i.e., sickness behavior, frailty, allostatic load, and/or palliative symptoms) of the experienced depressive symptoms and apathy, so we can determine which approach fits best per person. Taken together, to prevent or reduce poor outcomes such as HAD and mortality, depressive symptoms and apathy needs to better recognized during acute hospitalization and future interventions should initiate adequate follow-up care, as well as transitional care targeting not only physical aspects but also having more attention for the role of mental aspects: research to get the ball rolling.
Chapter 11

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