Depressive symptoms, apathy, and adverse health outcomes in acutely hospitalized older patients
Research to get the ball rolling
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“Going into hospital makes you sick.” Ms. Potthoff-Bennis (92), on her experience with an acute hospital admission.

Aging trends
The older population has been growing over the last few decades. The global proportion of adults aged 65 and older increased from 6.9% of the world’s population in 2000 (421 million) to 8.7% in 2017 (654 million). This percentage is estimated to nearly double, rising to almost 17% of the world’s population by 2050 (1.6 billion), whereas the total population is expected to grow by just 34% over the same period. In the Netherlands, the proportion of adults aged 65 and above increased by approximately 40%, from 13.6% of the total Dutch population in 2000 (2.2 million) to 18.8% in 2017 (3.2 million). Today, the global average life expectancy is increasing and living to the age of 70 or 80 is no longer a rarity in many parts of the world.

Acute hospitalization
While an increase in life expectancy among older adults is a positive change, the consequential demand for health care is also growing. Almost 10% of those aged 65 and above are acutely admitted to hospital annually. Acute hospitalizations in older people are a significant driver of increasing health care expenditure. Moreover, post-acute care expenses can be as high as the costs of the initial hospitalization. Approximately 70% of acutely hospitalized older patients demonstrated two or more acute illnesses and almost 90% two or more chronic diseases. Chronic diseases are defined as already existent before acute admission, of which hypertension, diabetes, and a solid tumor were most prevalent among acutely hospitalized older patients, and acute illnesses are defined as new diagnoses that required active treatment during hospitalization; of these, infection, acute renal failure, and anemia were the most common acute diseases among older medical patients. These medical illnesses among acutely hospitalized older patients are often accompanied by geriatric syndromes such as depressive symptoms, falls, and incontinence. Nevertheless, geriatric syndromes have remained loosely defined.

Geriatric syndromes
Geriatric syndromes refer to a multifactorial collection of symptoms common among older adults and across different disease categories. Generally, the term “syndrome” is used for a set of medical signs and symptoms that shows the existence of a particular disease, while geriatric syndromes refer to one symptom or a complex of symptoms with high prevalence in geriatric patients, as a result of multimorbidity (i.e., presence of two or more chronic conditions). Geriatric syndromes are common among older patients admitted to a hospital with an acute medical illness, and of these an average of six geriatric syndromes are identified at acute admission. Therefore such research is important, in particular, because the main focus of hospital care professionals is acute medical illness and ensuring the earliest discharge of patients, and as a result geriatric syndromes may be overlooked and remain after acute hospitalization; in these cases those syndromes are linked to adverse health outcomes post-discharge, including mortality and the loss of ability to perform one or more basic activities.
Adverse health outcomes after acute hospitalization among older adults

More than 30% of patients aged 65 and above admitted with an acute medical illness experience a loss of ability to perform one or more basic ADL during hospitalization, which may persist in a significant proportion during the post-hospitalization period. ADL is defined as common routine activities for resuming independent daily life and include dressing, using the toilet, bathing, eating, being mobile in and around the house, and transferring oneself out of bed. In the case where there is a loss of one or more ADL for the period during or after acute hospitalization, compared with the patient’s abilities two weeks prior to acute hospitalization, this functional decline has been signified as hospitalization-associated disability (HAD). Previous research has shown that the first post-discharge month is a key period for recovery because the absence of recovery from disabilities in this period predicts persistent disability and even all-cause mortality. Overall, the mortality rate after acute hospitalization was 41% of those developing new or additional ADL disabilities within one year of after acute hospitalization. Multiple factors can contribute to the development of HAD among older adults: Firstly pre-illness determinants of functional reserves (e.g., advancing age, poor mobility, and geriatric syndromes), which possibly result in a reduced capacity to recover from hospitalization; secondly, the severity of acute medical illness; thirdly, hospitalization-related factors such as restricted mobility, enforced dependence for ADL, undernutrition, and polypharmacy; fourth, post-hospitalization factors such as community support and quality of discharge planning. Additional factors to those mentioned here may also play a role but remain poorly researched. For example, little is known about the role of geriatric syndromes that have a strong psychological-behavioral component (e.g., depressive symptoms and apathy) in the development of and recovery from HAD and other adverse outcomes (e.g., unplanned readmission and mortality) within the critical post-discharge period.

Hospital-ADL study

Addressing this lack of information was one of the main reasons for launching the hospital-associated disability and impact on their daily life (Hospital-ADL) study, which was designed by an interdisciplinary team of researchers (e.g., psychologists, physical therapists, and nurses). In addition, the Hospital-ADL study aimed to investigate the course of physical functions (e.g., loss of muscle mass, muscle strength, and physical performance) and their association with adverse health outcomes. Moreover, the association of metabolic and pro-inflammatory factors with the development of and recovery from HAD was a research aim of the Hospital-ADL study. In October 2015, data collection began at the Amsterdam University Medical Centers location Academic Medical Center, and subsequently, patients were also recruited from six other Dutch hospitals. Data inclusion ended in June 2017, and data collection was completed in February 2018. Figure 1 provides an overview of the primary and secondary outcomes and the location of the data collection per time point of the Hospital-ADL study.
Depressive symptoms among the older population

Depressive symptoms are a common geriatric syndrome, with studies showing that more than one-third of older patients report clinically elevated depressive symptoms at acute admission. Depression is associated with adverse health outcomes among this population, including functional decline, and increased falls, readmissions, and mortality. There is ample evidence that elevated depressive symptoms among older adults are often not a transient phenomenon irrespective of the (clinical) setting. For example, among community-dwelling older adults or patients from mental health care facilities and general practitioners, between a third and a half of patients developed chronic cases with time point intervals of at least six months. This would suggest that likewise depressive symptoms post-hospitalization may not be a transient phenomenon, i.e., where most individuals recover with limited need for active intervention. However, Ciro et al. found that 19% of acutely hospitalized older patients reported new depressive symptoms three months post-discharge. The small number of existing longitudinal studies that focus on depressive symptoms during the critical first months after acute hospitalization have only performed a single post-hospitalization assessment, which makes it impossible to infer a course of duration. Addressing the dynamic nature of depressive symptoms during after acute hospitalization, which can be transient, increasing or persistent, by high temporal resolution analysis may provide useful information for acute hospital settings.

Symptomatology of depression

There is an increasing appreciation for the fact that depression is a highly heterogeneous disorder, within which marked inter-individual differences may exist in symptom patterns. These individual differences may be clinically meaningful, e.g., possibly predicting depression recovery and risk of unfavorable secondary outcomes including HAD and mortality. For example,
some studies have differentiated between two broad symptom categories of depression: somatic symptoms (e.g., poor appetite, fatigue, and insomnia) and cognitive-affective symptoms (e.g., anhedonia, negative thoughts, guilt, and hopelessness). Studies of cardiac patients distinguishing between these two symptom categories found a significant relationship between somatic depressive symptoms (but not between cognitive-affective) and adverse cardiac prognosis. In research focusing on older patients, these somatic depressive symptoms may be confounded by acute medical illness or features of the aging process. Hence, more frequently somatic diseases among older adults may be mistaken for somatic symptoms of depression, which can create a challenge for diagnosis. Although depressive symptoms appear to be a common debilitating condition among older adults, they are often undiagnosed and untreated. Effective treatment of depressive symptoms depends on their effective assessment. Among older patients with mild or no cognitive impairment, the Geriatric Depression Scale (GDS) is currently a preferred instrument for measuring depressive symptoms because it is specifically developed for a geriatric population, widely used in acute hospital settings, and predominantly includes cognitive-affective symptoms to rate probable depression among this population. However, within this cognitive-affective domain individual symptoms may, in addition, differentially predict outcomes.

Indeed, existing research has observed that specific cognitive-affective depressive symptoms such as apathy and hopelessness show a strong link with mortality. However, most of these studies focus on non-hospitalized adults and do not specifically consider adults of 60 and older. Therefore, little is known about the prevalence and predictive value of specific cognitive-affective depressive symptoms such as feelings of hopelessness and loss of energy among high-risk and older groups (e.g., acutely hospitalized older adults). Understanding depression heterogeneity and the specific cognitive-affective symptoms that predict adverse health outcomes among acutely hospitalized patients, may support the identification of individuals at elevated risk as well as those likely to benefit most from tailored interventions. For example, late-life depression is often mistaken for dementia (e.g., cognitive impairment and memory loss) and/or apathy, as it is highly correlated with diagnostic symptoms of depression such as loss of interest and initiative.

Apathy
Because of the highly correlated association between depressive symptoms and apathy, GDS furthermore incorporates apathy as one of the symptoms of depression. Still, apathy can be considered a construct distinguishable from depression. Apathy is defined as a concurrent reduction in cognitive, emotional, and motoric goal-directed behaviors and is one of the most common pervasive neuropsychiatric symptoms among older adults in general, becoming increasingly prevalent with aging. The presence of apathy is associated with an increased longitudinal risk of disability among older adults. However, little is known about the association of apathy with adverse outcomes in acutely hospitalized older patients.
Aims and outline of this thesis

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; second, by analyzing the longitudinal effects of depressive symptoms and their effects on adverse health outcomes; thirdly, by analyzing specific depressive symptoms (e.g., feelings of hopelessness) and specific symptoms of apathy (e.g., loss of interest).

Chapter 2 aims at a qualitative understanding of the experiences of acutely hospitalized older patients during the critical first 30 days post-discharge. Information gathered by semi-structured interviews is indicative as to which post-hospital symptoms patients tend to experience and as to the impact of these symptoms on resuming their daily routines after acute hospitalization. Chapter 3 sets out the design of the Hospital-ADL study, a longitudinal multicenter cohort study aimed at characterizing concomitants and predictors of adverse health outcomes, including HAD, unplanned readmissions, and mortality. This cohort study provides the data for all subsequent studies (i.e., chapters). Chapter 4 describes the prevalence and course of a broad spectrum of geriatric syndromes, from acute hospital admission to up to three months post-discharge. In addition, this study tests the probability of remaining or recovering from specific geriatric syndromes or of new syndromes developing after acute hospitalization, since most research has focused on geriatric syndromes during acute hospitalization.\(^7,\,57,\,58\)

Chapters 5 and 6 study the course of depressive symptoms among acutely hospitalized patients and the longitudinal association of these symptoms with adverse health outcomes post-discharge, at three months and then one year. Chapter 5 aims at determining if there are distinguishable trajectories of cognitive-affective depressive symptoms arising from acute hospitalization for up to three months post-discharge in older adults. In addition, this study investigates whether prognostic baseline variables are associated with inclusion in a trajectory group and if such distinct trajectories are associated with adverse health outcomes, including HAD, falls, unplanned readmissions, and mortality. Chapter 6 describes the longitudinal association between depressive symptoms and the ability to perform basic ADL and instrumental ADL (IADL). In addition, this element of the study disentangles the between-subject and within-subject components of depressive symptoms, making it possible to distinguish the association between variables among individuals and the association between variables as they change over time.

 Chapters 7 and 8 focus on the heterogeneity of depression and aim to determine if specific cognitive-affective symptoms predict adverse health outcomes among acutely hospitalized patients. Chapter 7 examines the role of specific depressive symptoms in mortality among acutely hospitalized older patients. Firstly the study describes the prevalence of specific depressive symptoms during the period of and after acute hospitalization. Secondly, since depressive symptoms may differ in their predictive value for mortality, this study, in addition
to researching the predictive value of the total GDS-15 score, aims to examine the predictive value of specific depressive symptoms for all-cause mortality in the three months post-discharge. Chapter 8 investigates the role of persistent symptoms of apathy in HAD in the critical first month after acute hospitalization, because persistent symptoms of apathy have been predictive of a loss of autonomy in ADL among older patients with Alzheimer’s disease. Therefore, this study investigates the prevalence of persistent symptoms of apathy among acutely hospitalized older patients from the time of discharge up to one month post-discharge and their predictive value for HAD. Additionally, this study aims to examine the predictive value of specific symptoms of apathy for HAD, focusing on the first three months post-discharge.

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, Chapters 9 and 10 focus on the role of motivational factors, such as depressive symptoms and apathy, on physical functioning and present the results of a systematic review of instruments for goal-setting in geriatric rehabilitation that could play an important part in motivation. Chapter 9 describes the relationship between general self-efficacy (GSE), which refers to “a broad and stable sense of personal competence in mastering a variety of stressful situations” (e.g., acute hospitalization), and functional recovery among acutely hospitalized older patients. Research has shown that GSE is linked with ADL limitations in older people and with motivational factors such as depressive symptoms and apathy. However, to our knowledge, little is known about the mutual influence of motivational factors on the existing relationship between GSE and poor functional outcomes among acutely hospitalized older patients. Chapter 10 presents a systematic review, which aims to evaluate the psychometric properties of goal-setting instruments applied within the field of geriatric rehabilitation.

Finally, Chapter 11 provides a general discussion of the main findings, discusses strengths and methodological limitations, and elaborates on implications both theoretical and relating to clinical practice and future research. Chapter 12 concludes the thesis with a summary in English and Dutch.
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Chapter 1


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