Apathy and cognitive decline in clinical studies of older persons

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CHAPTER I

General introduction and thesis outline

GENERAL INTRODUCTION

Cognitive decline and dementia

With the global rise in life expectancy, increasing numbers of older persons may present with complaints of impaired cognitive functioning (1). Memory deterioration in later life can be part of normal cognitive aging as well as be an early symptom of neurodegenerative and/or cerebrovascular disease, ultimately leading to dementia (2). Dementia is a chronic condition with loss of cognitive functioning and behavioral abilities to such a degree that these impairments interfere with a person's daily life and activities (3). Although currently no treatments are available for dementia (4), it is important to make a reliable differential diagnosis in older persons with cognitive complaints in primary care settings, in order to decide who needs further diagnostic work-up. Older persons with incipient dementia likely benefit from careful monitoring, timely referral to specialists, and advance care planning. On the other hand, older persons with memory complaints related to normal cognitive ageing (and their families), can be reassured. Therefore, it is important that reliable, easily accessible screening tools are available in general practice to identify older persons at increased risk for developing dementia or to reassure those who have complaints without unpropitious cognitive deficits.

Depression and apathy

When aiming to identify older persons with increased risk for developing dementia, general practitioners (GPs) also pay attention to other symptoms than cognitive decline. Previous research has shown that depressive symptoms in older persons are associated with an increased risk of developing dementia (5). It is unclear whether the association is mainly confined to a clinical diagnosis of depression, as a nominal entity, or part of a broader spectrum of depressive symptoms (on an ordinal scale). Most studies addressing this issue operationalized depressive symptoms as the score on a depression questionnaire, rather than clinical judgement of depression. Therefore, the psychometric characteristics and construct validity of the questionnaires that were used may have had unknown or even unforeseen negative impact on the results of these studies, especially when these have not been reported on extensively.

A clinical categorical diagnosis of depression according to de DSM-5 is based on several symptoms (3). Apathy can be one of those symptoms. While apathy can occur in the context of a depression, it may manifest independently as well. Originally, apathy has been defined as a syndrome of lack of motivation featured by goal-directed behavior, cognition and emotion (6). Apathy is common among community-dwelling older people and its prevalence is even higher among older persons with a diagnosis of mild cognitive impairment or dementia and among stroke survivors (7). Both apathy as an isolated symptom in the absence of affective symptoms as well as affective symptoms without apathy symptoms may be associated with an increased risk of dementia. Therefore,

it is important to delineate in detail the associations between scores on depression questionnaires and onset of dementia in relation to apathy symptoms and affective symptoms of depression.

Apathy and the Geriatric Depression Scale

The Geriatric Depression Scale (GDS) is a screening instrument that can be used to screen for depression symptoms among older persons, both in research and in clinical practice. The most commonly used version of the scale consists of 15 items, of which three have been considered to measure apathy symptoms rather than symptoms of a depressed mood (item 2: "Have you dropped many of your activities and interests?"; item 9: "Do you prefer to stay at home, rather than going out and doing things?"; item 13: "Do you feel full of energy?", with the latter being contra-indicative for apathy) (8). Multiple studies using factor analysis revealed these three items consistently load on the same factor (9). Therefore, specifically this questionnaire can help to assess differential associations between apathy or depressive symptoms and dementia, while questionnaires developed to measure specifically affective or apathy symptoms are less appropriate for this purpose.

Factor analyses, such as the ones identifying a cluster of three GDS items that appear to measure apathy, are able to identify items of a questionnaire that share common variance. In case the association between the overall score on the GDS and onset of dementia is driven by specific items that do not appear to form a separate cluster using factor analysis, other methods are needed to fully characterize this complex relationship. For this purpose, network analyses may be suitable as these are specifically appropriate to reveal by which individual items relationships between scores on questionnaires with other constructs are driven (10).

Apathy after stroke

Stroke increases the risk of dementia. Depending on the part of the brain affected by stroke and its severity, patients may experience cognitive decline and disability after a stroke. Stroke survivors often also face symptoms of depression and/or apathy (11). Previous research has shown that both depression and apathy after stroke are associated with more disability. Post-stroke apathy is also related to worse cognitive outcome, and due to the lack of motivation and goal-oriented behavior that characterizes apathy, it may also negatively impact the effect of rehabilitation programs (12). For instance, potential interactions between apathy and cognition may play an important role in the counseling of patients with respect to secondary prevention after the occurrence of a stroke. If symptoms of apathy and depression turn out to be independent determinants of cognitive decline, it will be important to address these constructs separately in rehabilitation treatment programs.

Combining data from different studies

Many population and clinical studies addressing complex constructs including apathy, depression and cognitive decline in older persons suffer from lack of power, because these measures were often used as secondary outcomes. Pooling datasets from multiple studies facilitates (sub-group) analyses with increased power. Pooling data, however, becomes difficult when variables have been collected in different ways, using a variety of measurement scales or different languages (13). Developing methods to recode variables that have been collected in different operational modes, could potentially solve the difficulties of pooling data from different sources. It is currently unknown to what extent such recoding processes might undermine the validity of the original variables, and subsequently negatively impact the validity of conclusions based on these recoded variables. It is also unknown what type of variables are specifically prone to loss of validity. Future studies may benefit from detailed analysis of this problem that, in a generic sense, is relevant to many studies with human participants.

THESIS OUTLINE

In this thesis, chapters II, III and IV consist of clinical studies based on data that were derived from the Prevention of dementia by intensive vascular care (preDIVA) trial (14). In brief, this was a cluster-randomized controlled trial which tested the efficacy of a nurse-led, multicomponent, cardiovascular intervention to prevent all-cause dementia among 3526 community-dwelling older persons who were aged 70 to 78 years at baseline. Patients with a (suspected) dementia diagnosis or other terminal illnesses at enrollment were excluded at baseline. Participants were recruited from 2006 to 2009 and were followed up to 8 years, with a median follow-up of 6.7 years. The control group received standard care, while, in addition, the intervention group visited a practice nurse every 4 months, who addressed all cardiovascular risk factors. Since the overall results of the main trial were neutral (15), the preDIVA data from both trial arms can be considered a single cohort and used for several post-hoc analyses.

In Chapter II we focus on the question which older persons' GPs should monitor or consider referring to a specialist when suspecting cognitive decline or when older persons themselves report memory problems. In this chapter, we show to what extent a combination of a single, dichotomous question on subjective memory complaints, the delayed recall item from the Mini-Mental State Examination (16) and a brief test of visual anterograde memory (17) may increase or decrease the risk of dementia. The question on subjective memory complaints was derived from the GDS, item 10: "Do you feel you have more problems with memory than most?".

In Chapter III all 15 items from the GDS were used to study whether symptoms of apathy, rather than depression, are associated with future dementia. The use of the GDS is appropriate for this research question, since several studies using factor analysis,

showed that three questions from the GDS load high on the same construct (mentioned above), which has been repeatedly used to measure apathy among older persons.

Factor analysis focusses on the shared variance of items, and therefore may be less useful in case the association between the GDS score and future dementia is driven by individual items rather than by groups of items. Therefore, in Chapter IV we used the GDS once more to study the association between apathy and depression items with future dementia, but this time using network analysis to reveal potential associations between individual GDS items and future dementia.

In Chapter V we report on the Apathy as New Outcome After Stroke (AENEAS) study. In this study, at six and 15 months post-stroke we assessed cognitive functioning using a short neuropsychological test battery and assessment instruments for apathy and depression, among stroke survivors with a mRS score of <= 3 (a mRS score of 3 indicates moderate disability) at three months post-stroke. With this design, we aimed to study the course of apathy after the acute phase of stroke and its relation with cognitive functioning.

In Chapter VI data were pooled from the preDIVA trial, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial (FINGER) (18) and the Multidomain Alzheimer Preventive Trial (MAPT) study (19). All three trials focused on the association between cardiovascular risk factors and cognitive decline or dementia. While pooling of data from different datasets may be desirable to increase power, it may be complicated also because of the differences in data collection of individual studies. Therefore, we investigate to what extent pooling of data results in information loss. Additionally, we studied the subsequent influence of this information loss on in-depth analyses in case recoded variables were used. Primarily, we focused on continuous variables that were recoded into dichotomous variables, such as the scores on different depression scales that were recoded into absence or presence of depression. More in-depth analyses are aimed at simulated continuous data that were recoded into dichotomous variables.

Chapter VII provides a general discussion of the preceding chapters, highlighting directions for future research and implications for clinical practice, and ending with the main conclusions that can be drawn from this thesis.

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