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PREVALENCE, SYMPTOMS AND RISK PROFILES OF APATHY AT OLD AGE

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PREVALENCE, SYMPTOMS AND RISK PROFILES OF APATHY AT OLD AGE

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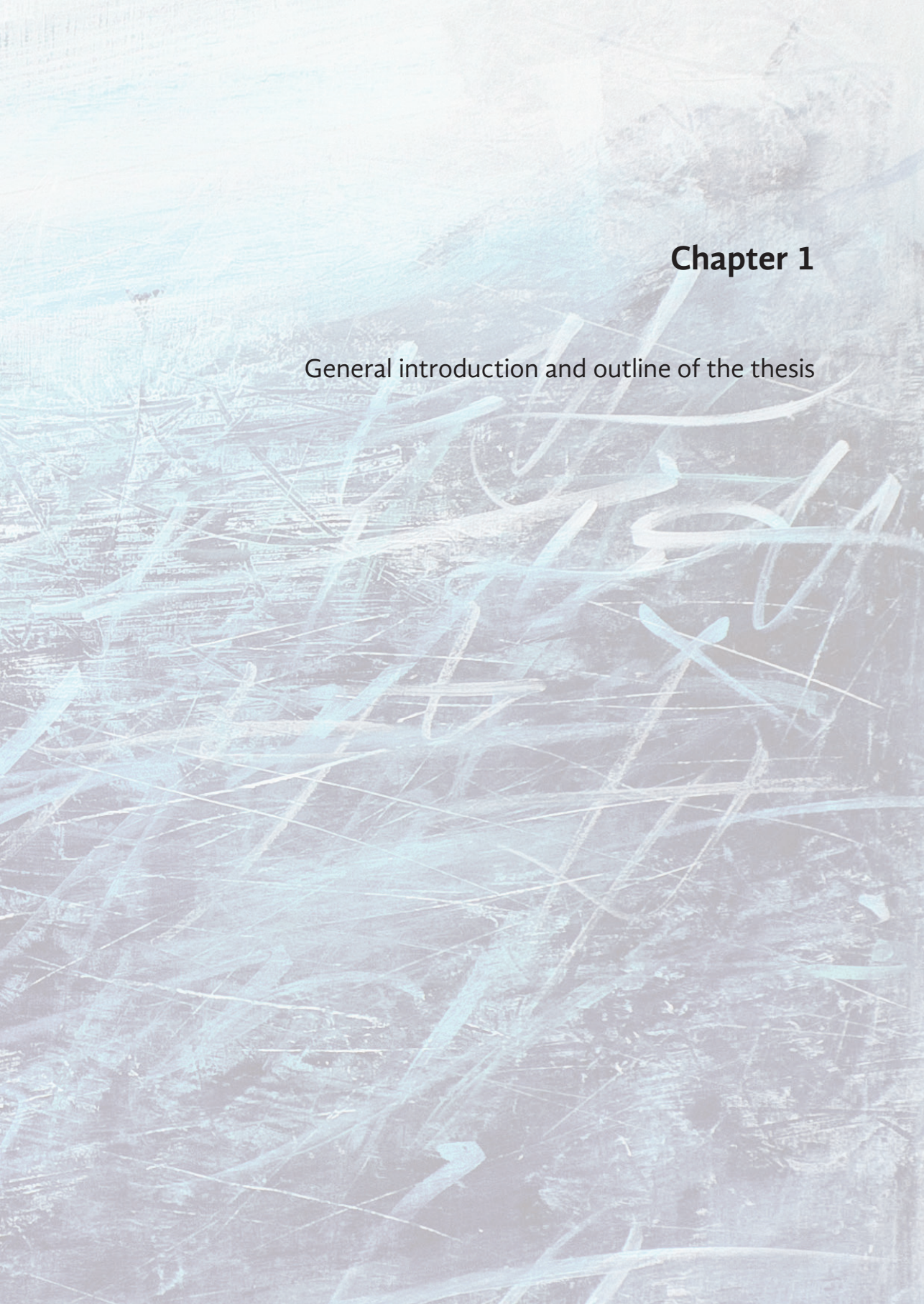
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The background of the page is an abstract composition of numerous overlapping brushstrokes. The strokes are primarily in shades of light blue and white, set against a darker, muted blue-grey background. The strokes vary in length, thickness, and direction, creating a sense of movement and texture. Some strokes are straight and diagonal, while others are curved or horizontal. The overall effect is a layered, painterly texture that covers the entire page.

Chapter 1

General introduction and outline of the thesis

Introduction

Case report

“Doctor, my husband just sits on the couch”.

Mr. A, a 73-year-old man, was admitted to the acute ward of our psychiatric hospital for older persons, because of a (first) depressive episode and suicidal ideation, after his brother-in-law had deceased. In the past months he had become much quieter, felt increasingly sad, lost interest in fishing (which he normally did four times a week), and slept poorly waking up at least 10 times during the night. He also lost about 10 pounds in weight and was becoming increasingly anxious, being convinced that he was suffering from a fatal disease. The last few weeks before hospital admittance, he thought about killing himself.

He was diagnosed with a first depressive episode with mood congruent psychotic symptoms. He was treated with nortriptyline 50 mg per day, with an adequate serum concentration, and olanzapine up to 20 mg per day. Recovery was slow and only after addition of lithium carbonate (400 mg per day) did his depression improve and the depressive symptoms disappear. Olanzapine was discontinued due to motor side-effects. After 3 months of hospitalization he was discharged and continued treatment in the psychiatry outpatient clinic. However, on one of the outpatient clinic appointments, his wife expressed her concern about the wellbeing of her husband, although he himself had no complaints. She mentioned that her husband had almost ceased to talk, lacked all initiative, and sat on the couch all day doing nothing. She was very worried because he seemed to be a different person: he had always been a very socially engaged and active person. According to the patient himself and his wife, he was no longer depressed; this, was also reflected in the score of 3 on the Geriatric Depression Scale.

This older man, showing lack of initiative, inactivity, lack of spontaneous speech, and the necessity for stimulation after remission of his depression, appears to suffer from apathy as a behavioral syndrome in its own right, especially since a sad mood and suicidal ideations are now absent.

The word ‘apathy’ has its origin in the old Greek ‘ἀπάθεια’ (apatheia), meaning ‘absence of feeling’. In the 3rd century before Christ, the Stoics believed that a human being could achieve true happiness when a condition free from ‘pathe’ in other words, free from emotions and passions was reached.¹ They thought that extreme emotions (such as fear, desire and pleasure) prevented humans from clear thinking and led them towards irrational behavior. The meaning of apathy changed in the early 20th century to that of a ‘state of non-reactivity’, both psychologically and physically.² Marin (1991) was the first to conceptualize apathy in its currently accepted significance.² He described apathy as a lack of motivation that was not attributable to a diminished level

of consciousness, intellectual deficit or emotional distress. He also developed diagnostic criteria for apathy that included a lack of motivation as the cardinal symptom with concomitant diminished goal-directed behavior (lack of effort, initiative, perseverance, and productivity), diminished goal-directed cognition (lack of interest, concern and awareness about one's personal, health, or financial problems), and diminished emotions (unchanging affect, lack of emotional responsivity to positive or negative events, and absence of excitement). Starkstein et al (2008) modified these diagnostic criteria into a more standardized set by adding i) the time period of 4 weeks in which, most of the time, symptoms should be present; ii) the necessity of experiencing functional impairment in different areas of daily living; and iii) by omitting the criterion that there should be an absence of a depressive disorder or cognitive decline.³

Apathy may be part of the symptomatology of many different neuropsychiatric disorders including cognitive decline and dementia, Parkinson's disease, Huntington's disease and, major depression, and may follow stroke. Several neuroanatomical and neurofunctional clinical studies have shown an association between the presence of apathy and pathology of the fronto-subcortical neuronal network and anterior cingulate cortex (ACC) in the brain (figure 1), such as reduced grey matter volume and decreased metabolic activity of the ACC.⁴⁻⁶ Although apathy most often occurs as one of the symptoms of the abovementioned neuropsychiatric disorders, it is also found as a distinct behavioral syndrome, with its own cluster of symptoms, co-occurring with these disorders, but having a more prominent position.⁷⁻¹³ However, apathy is sometimes present even in the absence of these morbidities.

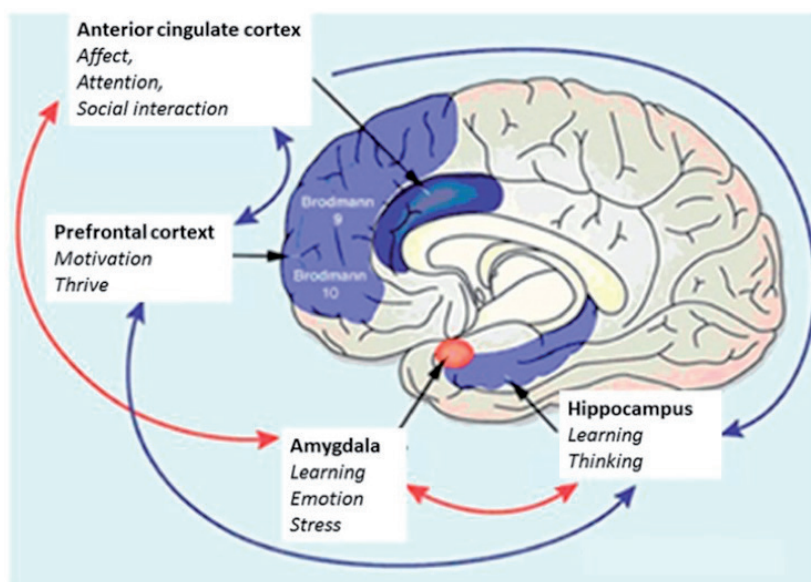


Figure 1. Anterior cingulate cortex as part of the corticolimbic system

Cross-sectional studies found that a higher age,^{7,10} having no partner and/or living alone,^{8,14} male gender,^{7,15} cognitive impairment,⁸ and cardiovascular diseases¹⁶ were risk factors for the presence of apathy. In longitudinal studies on apathy in old age a higher age,^{13,17} male gender,¹³ cognitive impairment,^{13,15,17,18} the presence of depressive symptoms^{8,9} and the presence of cardiovascular disease including stroke and/or risk factors for cardiovascular disease appeared to be predictive of future apathy.^{9,17}

Apathy is associated with decreased daily functioning,^{17,19} a subjectively decreased quality of life as well as adverse health outcomes including a higher mortality and less likelihood to benefit from rehabilitation services and treatment.^{13,19-24}

Assessment of apathy

Marin was the first to develop an instrument to assess apathy, i.e. the Apathy Evaluation Scale (AES). The AES consists of three versions; a patient-rated version, a clinician-rated version, and a caregivers-rated version.²⁵ However, no conclusive threshold values of the AES for clinically relevant apathy are established.²⁶ Starkstein abbreviated the Apathy Evaluation Scale into the Apathy Scale (appendix), with proposed cut-offs for clinically relevant apathy based on research in a clinical population with Parkinson's disease.²⁷ Apart from these two scales, several other instruments have been developed to specifically assess apathy such as the Dementia and Apathy Interview Rating scale; the Apathy Inventory; and the Lille Apathy Rating Scale.²⁸⁻³⁰ In addition, several (more general) assessment tools include items to screen for symptoms of apathy such as the Neuropsychiatric Inventory, the Brief Psychiatric Rating Scale, and the Frontal Systems Behavior Scale.²⁶ It is possible that different combinations of apathy symptoms indicate different apathy subtypes that are related to specific characteristics and, therefore, require distinct treatment approaches.^{31,32} However, no studies have empirically examined possible subtypes of apathy in relation to specific patient and clinical characteristics. With data-driven techniques such as Latent Class Analyses (LCA) that cluster persons based on a given clinical outcome, an empirically based classification of apathy may be obtained that enables the identification of distinct subtypes of apathy.

Apathy and late-life depression

Apathy is a well-known symptom of late-life depression. However, apathy can also occur as a distinct behavioral syndrome in depression, when playing a prominent role in its phenomenology. In older persons suffering from depression, apathy as a distinct behavioral syndrome was present in 38-96%.^{19,33,34}

After an international consensus meeting the following definition and criteria were formulated (see table 1): Apathy as a clinically relevant syndrome consists of a cluster of clinical features including a (severe) loss of motivation and interest, and a significant decreased goal directed behavior, emotional responsivity and cognitive activity.^{2,3,35,36} Differentiating between apathy and depression can be a challenge, since key symptoms

of both these disorders show considerable overlap. However, apathy is a motivational disorder, lacking mood-related symptoms, whereas depression is primarily a mood disorder.³⁷⁻³⁹ It is unknown whether (or not) the presence and severity of apathy differs between early-life depression and late-life depression.

There is evidence that apathy and depression have different etiologies, risk factors, pathophysiology and outcomes. Immune activation, as indicated by higher C-reactive protein (CRP) concentrations, has been associated with more apathy symptoms but not with depression, although the results from different studies were inconclusive.^{9,12,16} Moreover, longitudinal studies show that cardiovascular disease and cardiovascular risk factors predict the occurrence of apathy, but not of depressive symptoms.^{9,16} Neuro-radiological research with MRI-scanning showed that both apathy and depression were associated with reduced gray matter volumes, but in different areas of the brain.^{40,41} Also, fMRI-scans revealed that resting functional connectivity of the nucleus accumbens (NAcc) and the dorsal anterior cingulate (dACC) distinguished older depressed persons with apathy from older depressed persons without apathy and from healthy older persons.⁴² In addition, treatment outcome of apathy differs from that of depression in that antidepressants effectively treat depression but not apathy,^{19,40,41} and that in depressed older patients, apathy is a predictor of poor response to antidepressive therapy,^{20,40,43} of chronicity of depression, and of more severe disability.¹⁹

Burden of apathy

The presence of apathy can be extremely distressing for caregivers compromising their quality of life.^{8,44,45} It is often suggested that caregivers of patients with apathy suffer more than the patients themselves, due to the frequent lack of awareness and insight in patients with apathy. However, to date, very few studies have investigated the quality of life in older persons suffering from apathy. In a study including a Japanese population-based older population, apathy was not associated with a diminished quality of life;⁴⁶ this is in contrast to findings in clinical populations suffering from dementia, in which apathy was associated with decreased subjectively perceived quality of life.⁴⁷⁻⁴⁹

Study cohorts used in this thesis

Netherlands Study of Depression in Older Persons (NESDO)

NESDO is an ongoing prospective cohort study that aims to examine the determinants, long-time course and the consequences of depression in late life.⁵⁰ Between 2007 and 2010, 378 older persons with a depressive disorder in the previous 6 months before baseline assessment and diagnosed according to the DSM-IV criteria, and 132 non-depressed older persons, were included in the NESDO baseline sample (total sample n=510, aged 60-93 years). Participants were recruited from primary health care practices and mental health care institutes to create a sample that represents all stages of depression. Participating primary health-care practices were from the regions

Table 1. Diagnostic criteria for apathy

For a diagnosis of Apathy the patient should fulfil the criteria A, B, C and D	
A	Loss of or diminished motivation in comparison to the patient’s previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.
B	Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time
Domain B1:	Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following: – Loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices) – Loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities)
Domain B2:	Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following: – Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs). – Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the persons residence, neighbourhood or community)
Domain B3 :	Loss of, or diminished, emotion as evidenced by at least one of the following: – Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect) – Loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)
C	These symptoms (A-B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.
D	The symptoms (A-B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).

Amsterdam, Leiden and Groningen, and participating mental health-care institutes are the GGZ inGeest and the VUMC in Amsterdam, the LUMC and GGZ Rivierduinen and Parnassia in Leiden, the UMCG and Lentis in Groningen, the GGNet in Apeldoorn and Zutphen, and the RadboudUMC and GGZ Nijmegen in Nijmegen. Excluded were persons with a Mini-MentalState Examination score (MMSE) <18, a primary diagnosis of dementia, a psychotic disorder, obsessive-compulsive disorder or severe addiction disorder, or insufficient command of the Dutch language. During a 4-hour baseline assessment consisting of written questionnaires, interviews, a medical examination, a cognitive

computer task and collection of blood and saliva samples, a wide range of information was obtained with respect to health outcomes, demographic, psychosocial, clinical, biological and genetic characteristics. Data obtained from the baseline assessment are used in our cross-sectional studies. Every six months, severity of depressive symptoms was monitored with the Inventory of Depressive Symptomatology Self-Report (IDS-SR) that was sent to all participants. Between 2009 and 2012, a second extensive face-to-face assessment was performed. Because of attrition, only 285 of the 378 depressed older persons at baseline participated in the 2-year follow-up. Data obtained from the 2-year follow-up assessment are used in our longitudinal study.

The Netherlands Study of Depression and Anxiety (NESDA)

The Netherlands Study of Depression and Anxiety (NESDA) has almost the same study design as NESDO being a multi-site naturalistic 8-year longitudinal cohort study, among 2,981 participants aged 18 through 65 years.⁵¹ Aims of this study were to: 1) describe the long-term course and consequences of depressive and anxiety disorders, and 2) integrate biological and psychosocial research paradigms within an epidemiological approach to examine (interaction between) predictors of the long-term course and consequences. The sample consists of 1,701 persons with a current (6 month recent) diagnosis of depression and/or anxiety disorder, 907 persons with life-time diagnoses, or at risk because of a family history or sub-threshold depressive or anxiety symptoms, and 373 healthy controls. Participants were recruited from general practices and mental healthcare organizations. During a 4-hour baseline assessment including written questionnaires, interviews, a medical examination, a cognitive computer task and collection of blood and saliva samples, extensive information was gathered about key (mental) health outcomes and demographic, psychosocial, clinical, biological and genetic determinants. Detailed assessments were repeated after 1, 2, 4 and 8-years follow-up. Wave 6 data (follow-up after 6 years, in which the Apathy Scale was assessed) are used in our study investigating apathy in late-life depression compared to early-life depressed persons.

Proactive Management of Depression in the Elderly (PROMODE)

The primary aim of the Proactive Management of Depression in the Elderly (PROMODE) study, a randomized controlled trial, was to investigate the (cost-) effectiveness of a combined screening and treatment program for older persons aged ≥ 75 years with depressive symptoms, in general practices in the Leiden region.⁵² Therefore, 11,635 registered subjects aged ≥ 75 years, in 67 general practices in the Leiden region were invited for screening at home for depressive symptoms, from April 2007 until July 2008. Exclusion criteria were current treatment for depression, clinical diagnosis of dementia, or a Mini-Mental State Examination (MMSE) score < 19 points, loss of a partner or child in the preceding 3 months, life expectancy ≤ 3 months, and not

speaking Dutch. Screening yielded 264 screen-positive persons according to a ≥ 5 -point score on an interviewer-administered 15-item version of the Geriatric Depression Scale (GDS-15). Of those, 2,393 persons gave written informed consent to participate in the randomized trial. By means of interviews and written questionnaires information was collected on sociodemographic, clinical and quality-of-life determinants. Data from 1,118 persons were used in our study on apathy and quality of life. Further, data from 120 persons suffering from clinically relevant apathy were used in our study examining the occurrence of relevant subtypes of apathy.

Background and aims of this study

The aim of the work described in this thesis is to investigate different aspects of apathy - as a distinct clinical syndrome - in older persons with and without concurrent depression. The primary objectives are to assess prevalence, incidence, course, correlates and predictors of apathy, particularly in depressed older persons. Secondary objectives are to determine relevant subtypes of apathy and their associating correlates using Latent Class Analyses, the presence and associating factors of clinically relevant apathy in older depressed persons compared to younger depressed persons, and the impact of clinically relevant apathy on quality of life.

In this thesis the following research questions are addressed:

1. *Is it possible to distinguish clinically relevant subtypes of apathy in persons with apathy according to the Apathy Scale using specific data-driven Latent Class Analyses?*
2. *What is the prevalence, severity and clinical profile of apathy in depressed and non-depressed older persons and does apathy relate to severity of depression or other variables?*
3. *Which characteristics predict the incidence and course of apathy in depressed older persons over a 2-years period?*
4. *Is apathy - as a distinct clinical syndrome - also present in depressed younger adults and what are the associating factors in comparison to those in depressed older persons?*
5. *Is apathy associated with diminished quality of life among community-dwelling older persons, irrespective of depression and/or impaired cognition?*

Outline of this thesis

In **Chapter 2**, the aim is to determine clinically relevant subtypes of apathy according to the Apathy Scale in older persons who were included in the PROMODE study using data-driven Latent Class Analysis (LCA), and to investigate specific characteristics across the classes identified by LCA. Then, in **Chapter 3**, the prevalence, severity and clinical profile of apathy in depressed and non-depressed older persons, in relation to various possible determinants, is assessed in the NESDO participants. **Chapter 4** examines which characteristics predict the incidence and course of apathy as a distinct

behavioral syndrome, in older persons in the NESDO study who were depressed at baseline, over a 2-year period. Then, using data of the NESDO and NESDA, **Chapter 5** explores whether apathy more frequently occurs in late-life depression compared to early-life depression. In addition, various determinants of clinically relevant apathy in older compared to younger depressed persons are assessed. **Chapter 6** investigates in the PROMODE study whether the presence of apathy among community-dwelling older persons is associated with a diminished quality of life. Finally, **Chapter 7** places our findings in a current perspective, discusses clinical implications, and makes some recommendations for future research.

References

1. Lidell HGaS, Robert. A Greek-English Lexicon. revised and augmented throughout. Oxford: Clarendon press.; 1940.
2. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci.* 1991;3:243-254.
3. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry.* 2008;79:1088-1092.
4. Starkstein SE, Mizrahi R, Capizzano AA, Acion L, Brockman S, Power BD. Neuroimaging correlates of apathy and depression in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci.* 2009;21:259-265.
5. Lavretsky H, Ballmaier M, Pham D, Toga A, Kumar A. Neuroanatomical characteristics of geriatric apathy and depression: a magnetic resonance imaging study. *Am J Geriatr Psychiatry.* 2007;15:386-394.
6. Alexopoulos GS, Hoptman MJ, Yuen G, et al. Functional connectivity in apathy of late-life depression: a preliminary study. *J Affect Disord.* 2013;149:398-405.
7. Adams KB. Depressive symptoms, depletion, or developmental change? Withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *Gerontologist.* 2001;41:768-777.
8. Onyike CU, Sheppard JM, Tschanz JT, et al. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry.* 2007;15:365-375.
9. van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry.* 2008;23:266-271.
10. Mehta M, Whyte E, Lenze E, et al. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *Int J Geriatr Psychiatry.* 2008;23:238-243.
11. Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry.* 2008;23:170-177.
12. Maas DW, van der Mast RC, de Craen AJ. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry.* 2009;24:1177-1184.
13. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int Psychogeriatr.* 2010;22:426-436.
14. Clarke DE, van Reekum R, Simard M, et al. Apathy in dementia: clinical and sociodemographic correlates. *J Neuropsychiatry Clin Neurosci.* 2008;20:337-347.
15. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr.* 2010;22:819-829.

16. Ligthart SA, Richard E, Fransen NL, et al. Association of Vascular Factors With Apathy in Community-Dwelling Elderly Individuals. *Vascular Factors and Apathy. Arch Gen Psychiatry.* 2012;69:636-642.
17. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - the Sydney Stroke Study. *Psychol Med.* 2005;35:1707-1716.
18. Tatsch MF, Bottino CM, Azevedo D, et al. Neuropsychiatric symptoms in Alzheimer disease and cognitively impaired, nondemented elderly from a community-based sample in Brazil: prevalence and relationship with dementia severity. *Am J Geriatr Psychiatry.* 2006;14:438-445.
19. Yuen GS, Bhutani S, Lucas BJ, et al. Apathy in Late-Life Depression: Common, Persistent, and Disabling. *Am J Geriatr Psychiatry.* 2015;23:488-494.
20. Levkovitz Y, Sheer A, Harel EV, et al. Differential effects of deep TMS of the prefrontal cortex on apathy and depression. *Brain Stimul.* 2011;4:266-274.
21. Lenze EJ, Skidmore ER, Dew MA, et al. Does depression, apathy or cognitive impairment reduce the benefit of inpatient rehabilitation facilities for elderly hip fracture patients? *Gen Hosp Psychiatry.* 2007;29:141-146.
22. Lavretsky H, Zheng L, Weiner MW, et al. Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. *Am J Psychiatry.* 2010;167:589-597.
23. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 2006;77:8-11.
24. Resnick B, Zimmerman SI, Magaziner J, Adelman A. Use of the Apathy Evaluation Scale as a measure of motivation in elderly people. *Rehabil Nurs.* 1998;23:141-147.
25. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res.* 1991;38:143-162.
26. Weiser M, Garibaldi G. Quantifying motivational deficits and apathy: a review of the literature. *Eur Neuropsychopharmacol.* 2015;25:1060-1081.
27. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 1992;4:134-139.
28. Strauss ME, Sperry SD. An informant-based assessment of apathy in Alzheimer disease. *Neuropsychiatry Neuropsychol Behav Neurol.* 2002;15:176-183.
29. Sockeel P, Dujardin K, Devos D, Deneve C, Destee A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2006;77:579-584.
30. Robert PH, Clairet S, Benoit M, et al. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int J Geriatr Psychiatry.* 2002;17:1099-1105.

31. Starkstein SE. Apathy in Parkinson's disease: diagnostic and etiological dilemmas. *Mov Disord.* 2012;27:174-178.
32. Pedersen KF, Alves G, Larsen JP, Tysnes OB, Moller SG, Bronnick K. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *Am J Geriatr Psychiatry.* 2012;20:142-148.
33. Wongpakaran N, van Reekum R, Wongpakaran T, Clarke D. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Ann Gen Psychiatry.* 2007;6:7.
34. Lampe IK, Heeren TJ. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *Int Psychogeriatr.* 2004;16:481-486.
35. Robert P, Onyike CU, Leentjens AF, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry.* 2009;24:98-104.
36. Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry.* 2011;26:158-165.
37. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord.* 1993;28:117-124.
38. Leontjevas R, Teerenstra S, Smalbrugge M, et al. More insight into the concept of apathy: a multidisciplinary depression management program has different effects on depressive symptoms and apathy in nursing homes. *Int Psychogeriatr.* 2013;25:1941-1952.
39. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci.* 1998;10:314-319.
40. Lavretsky H, Lesser IM, Wohl M, Miller BL, Mehringer CM. Clinical and neuroradiologic features associated with chronicity in late-life depression. *Am J Geriatr Psychiatry.* 1999;7:309-316.
41. Yuen GS, Gunning FM, Woods E, Klimstra SA, Hoptman MJ, Alexopoulos GS. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *J Affect Disord.* 2014;166:179-186.
42. Alexopoulos GS, Hoptman MJ, Kanellopoulos D, Murphy CF, Lim KO, Gunning FM. Functional connectivity in the cognitive control network and the default mode network in late-life depression. *J Affect Disord.* 2012;139:56-65.
43. Chaturvedi SK, Sarmukkaddam SB. Do negative symptoms influence outcome of depression? *Indian J Psychiatry.* 1986;28:305-310.
44. Thomas P, Clement JP, Hazif-Thomas C, Leger JM. Family, Alzheimer's disease and negative symptoms. *Int J Geriatr Psychiatry.* 2001;16:192-202.
45. Kaufer DI, Cummings JL, Christine D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc.* 1998;46:210-215.

46. Yamashita K, Iijima K, Kobayashi S. Relationship among activities of daily living, apathy, and subjective well-being in elderly people living alone in a rural town. *Gerontology*. 1999;45:279-282.
47. Samus QM, Rosenblatt A, Steele C, et al. The association of neuropsychiatric symptoms and environment with quality of life in assisted living residents with dementia. *Gerontologist*. 2005;45 Spec No 1:19-26.
48. Yeager CA, Hyer L. Apathy in dementia: relations with depression, functional competence, and quality of life. *Psychol Rep*. 2008;102:718-722.
49. Gerritsen DL, Jongenelis K, Steverink N, Ooms ME, Ribbe MW. Down and drowsy? Do apathetic nursing home residents experience low quality of life? *Aging Ment Health*. 2005;9:135-141.
50. Comijs HC, van Marwijk HW, van der Mast RC, et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res Notes*. 2011;4:524.
51. Penninx BW, Beekman AT, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res*. 2008;17:121-140.
52. van der Weele GM, de Waal MW, van den Hout WB, et al. Yield and costs of direct and stepped screening for depressive symptoms in subjects aged 75 years and over in general practice. *Int J Geriatr Psychiatry*. 2011;26:229-238.



Chapter 2

Latent Class Analysis of the Apathy Scale does not identify subtypes of apathy in general population-based older persons

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Abstract

Objectives: To identify clinically relevant subtypes of apathy in older persons using Latent Class Analysis (LCA) and investigate the distribution of different characteristics across these subtypes.

Measurements: Cross-sectional data of 122 older persons (mean age 84 years, 60% female) participating in the general population-based PROactive Management Of Depression in the Elderly (PROMODE) study, with apathy according to a score of 14 or higher on the Apathy Scale, were included for LCA. All 14 items of the Apathy Scale were used as indicator variables. Several characteristics were examined including sociodemographics; depressive and anxiety symptoms; global cognitive function; quality of life indicators; hazardous alcohol intake (drinking ≥ 14 consumptions per week); and perceived chronic pain.

Results: Three distinct LCA classes were found classifying 17%, 7% and 76% of the participants, respectively. Individuals in the first class had a higher level of education and were less likely to live alone. Those in the second class had higher apathy and depression scores, lived more frequently alone and used more alcohol. Individuals in the third class showed a lower level of education and worse cognitive function. In multivariable multinomial analyses, only a lower educational level and higher scores on the Apathy Scale were significant predictors for class membership.

Conclusion: Differences between LCA-derived classes were minimal, suggesting that in a general population-based cohort the Apathy Scale measures a homogeneous construct.

Introduction

Apathy is an important behavioral syndrome of several late-life neuropsychiatric disorders, such as depression and dementia.¹⁻⁴ The main clinical feature of apathy is diminished motivation, as is apparent from a lack of goal-directed behaviour, and cognition and/or emotions that lead to functional impairments.⁵⁻⁷ The presence of apathy is associated with worse daily functioning, higher mortality, less likelihood to benefit from rehabilitation services, and poorer perception of quality of life.⁸⁻¹⁴

In community-based older populations the prevalence of apathy was found to range from 6–51%.^{3;15-21} Risk factors for apathy include increasing age,^{15-17;19;20} having no partner and/or living alone,³ male gender,¹⁶ lower level of education,^{9;16} cognitive impairment,^{3;16;22} depressive symptoms,^{3;16;21} and cardiovascular disease (CVD) including stroke and/or risk factors for CVD.^{8;17;21;23}

Separate classes of apathy may indicate different apathy subtypes that are related to specific characteristics and, therefore, require distinct treatment approaches.²⁴ However, no studies have empirically examined possible subtypes of apathy in relation to specific characteristics. Most studies on characteristics of apathy used the total apathy scores for the analysis of associations, thereby ignoring possible heterogeneity within the apathy syndrome. The use of total scale scores makes it impossible to detect possible associations between a particular determinant and presumed subtypes,²⁵ which could also apply to the Apathy Scale. Furthermore, instruments not primarily developed for the assessment of apathy (e.g. the Neuropsychiatric Inventory and the 3-item version of the Geriatric Depression Scale-15) have often been used.^{16;20;21;23}

Free from any *a priori* assumption, data-driven techniques such as LCA that cluster persons based on a given outcome, may result in an empirically based classification and enable to identify distinct subtypes of apathy. Therefore, this study aimed to identify clinically relevant subtypes of apathy using LCA in 122 older persons participating in the community-based PROactive Management Of Depression in the Elderly (PROMODE) study. All participants had to have apathy according to a minimum score of 14 on the Apathy Scale. This study also investigated whether specific characteristics were present across the LCA-identified classes of apathy.

Methods

Study design

Data were obtained from the baseline assessment of the PROMODE study. This randomized controlled trial investigated the (cost-) effectiveness of a combined screening and treatment program for older persons aged ≥ 75 years with untreated depressive symptoms in 73 general practices in the Leiden region (the Netherlands).²⁶

From April 2007 to July 2008, all registered persons aged ≥ 75 years in these 73 general practices were invited for screening at home for depressive symptoms. Exclusion criteria were: current treatment for depression, a clinical diagnosis of dementia or a Mini-Mental State Examination (MMSE) score < 19 points, loss of partner or child in the preceding 3 months, terminal illness with a life expectancy of ≤ 3 months, and not speaking Dutch. Informed consent was obtained from all participants.

From the original 2759 study population 366 persons were excluded for the following reasons: a life expectancy of ≤ 3 months ($n=22$), current treatment for depression ($n=141$), loss of partner ≤ 3 months ago ($n=21$), a diagnosis of dementia ($n=114$), and various other reasons ($n=68$). Of the 2393 invited persons, 1054 were non-respondents (response rate 56%) and 101 persons were excluded before/during the baseline interview because of current treatment for depression, severe cognitive impairment (MMSE baseline score < 19 points), and for other reasons. Another 120 persons were excluded because of inadequate or missing data, resulting in 1118 persons with complete data on the Apathy Scale scores. Apathy, according to a score of 14 or higher on the Apathy Scale,²⁷ was found in 122 persons, who were included in the present sub-study. When comparing non-respondents ($n=1174$) to included participants ($n=1118$) of the PROMODE study, we found no differences with respect to sex ($p=0.84$) and age group ($p=0.54$).

Apart from the exclusion criteria 'current treatment for depression' GP's were asked to give their clinical judgement about the presence of depressive symptoms. GP's judgement on the presence of (possible) depression was higher in non-respondents compared to respondents (respectively 24% and 18%, $p<0.005$). Unfortunately, among non-respondents no information about apathy was available.

This study was approved by the Medical Ethical Committee of the Leiden University Medical Centre.

Measures

Assessment of apathy

Apathy was assessed using the 14-item Apathy Scale,²⁷ which is an abbreviation of the Apathy Evaluation Scale.²⁸ The Apathy Scale consists of 14 items with scores ranging from 0-3 points per item (maximum score of 42), with higher scores indicating more severe apathy.²⁷ For the LCA, all 14 items of the Apathy Scale were used as indicator variables and dichotomised as follows: absence of an item (score of 0 or 1) and presence of an item (score 2 or 3).

Assessment of possible characteristics for apathy

To characterize the LCA-identified classes of apathy, several characteristics were used including sociodemographics; depressive and anxiety symptoms; global cognitive function; quality of life indicators; hazardous alcohol intake (drinking ≥ 14 consumptions

per week); and perceived chronic pain (assessed with one item of the Short-Form 36 Health Survey). The 15-item Geriatric Depression Scale (GDS-15) was administered as a screening instrument for depressive symptoms.^{29;30} The score of the GDS-15 ranges from 0 to 15 points with higher scores indicating more depressive symptoms.^{31;32} Presence of anxiety was measured using the 7-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) with scores ranging from 0 to 21 points and higher scores indicating more symptoms of anxiety.^{33;34} Global cognitive functioning was assessed with the MMSE using total scores. The MMSE is a screening instrument with a good inter-rater and test-retest reliability.³⁵⁻³⁷

Overall quality of life was assessed using Cantril's Ladder, which is a visual analogue scale with scores ranging from 1 to 10 and higher scores indicating better experienced quality of life.³⁸ Subjective health quality was measured with the EuroQol (EQ)-5D thermometer,³⁹ scored from 0 to 100 with a higher score indicating better quality of life.⁴⁰ Perceived loneliness was assessed with the De Jong-Gierveld Loneliness questionnaire consisting of 6 items; scores ≥ 2 indicated the presence of perceived loneliness and a maximum score of 6 indicates more severe loneliness.^{41;42}

Statistical analyses

Data are presented as numbers with percentages, means with standard deviations (SD), and median with interquartile ranges (IQR), where appropriate.

To investigate the presence of subtypes of apathy, LCA was used. LCA (often described as the 'categorical equivalent' of factor analysis) assumes that an unobserved, latent categorical variable explains the association between a set of observed symptoms. Mixture models, like LCA, are extensively described in an earlier report.⁴³ The LCAs were conducted using M-plus version 5.⁴⁴ To determine which model best fitted the data, we examined the Bayesian Information Criterion (BIC), sample size adjusted BIC (ssaBIC), entropy, the Lo-Mendell-Ruben (LMR) likelihood ratio test, the proportion of respondents in each class, and the interpretability and clinical relevance of the latent classes. Lower BIC and ssaBIC values indicate better model fit. The LMR provides a p-value, which indicates whether the k-1 class model is rejected in favour of the k class model. Entropy, as a measure of the quality of classification, is presented for models with more than one class and ranges from 0 to 1 with values closer to 1 indicating greater classification accuracy. Finally, the proportions of individuals in each class are presented. To identify clinically relevant classes, we aimed to recognize classes with > 5% of the sample. Currently, there is no consensus as to which criterion identifies the best fitting number of classes.

After identification of the classes, persons were assigned to their most likely class based on model probabilities. For dichotomous variables, Chi-square statistics or Fisher's exact test (where appropriate), and for continuous variables Kruskal-Wallis non-parametric test, were used to test differences in the distribution of characteristics between classes.

Additional pairwise comparisons were performed to test for differences between pairs of classes. A p-value < 0.05 was considered statistically significant. To further test the association between the characteristics and the classes, we conducted multivariate multinomial logistic regression analyses by entering variables that showed a significance level of $p < 0.1$ in the Chi-square or Kruskal-Wallis tests, next to age and gender that were forced into the model. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed. A p-value < 0.05 was considered statistically significant. All comparisons were conducted using SPSS version 21.0 for Windows (SPSS INC., 2012).

Results

Demographic and clinical characteristics

Table 1 presents the sociodemographic and clinical characteristics of the 122 older persons with an Apathy Scale score ≥ 14 points.

Table 1. Characteristics of the study population (n=122)

Sociodemographic characteristics		
Age in years, mean (SD)	82	(5)
Female gender, n (%)	74	(61)
Low level of education, n (%) ^a	58	(48)
Living alone, n (%)	80	(66)
Clinical characteristics		
Alcohol use > 14 drinks/week, n (%)	12	(10)
Presence of chronic pain, n (%)	67	(55)
Quality of life		
Cantril's Ladder score, median (IQR)	7	(6-8)
EuroQol-5D thermometer score, median (IQR)	65	(50-76)
De Jong-Gierveld Loneliness score, median (IQR)	2	(1-3)
De Jong-Gierveld Loneliness score ≥ 2 , n (%)	65	(53)
Neuropsychiatric characteristics		
Apathy Scale score, median (IQR)	16	(14-18)
Geriatric Depression Scale score, median (IQR)	2.5	(1-4)
Hospital Anxiety Scale-Anxiety score, median (IQR) ^b	2	(0.8-4)
Mini-Mental Status Examination score, median (IQR) ^c	27	(24-29)
<i>Notes:</i> Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate. ^a Maximum of 6 years of schooling; ^b Anxiety subscale of the Hospital Anxiety Depression Scale; ^c Persons with a Mini-Mental Status Examination score < 19 were excluded.		

This study population had a mean age of 82 (SD=5, range 75-96) years, 74 (61%) of them were female, the median score on the GDS-15 was 2.5 (IQR 1-4) and the median score on the MMSE was 27 (IQR 24-29).

Latent class analyses

The parameters of fit and the proportion of individuals in each class of the LCA are presented in Table 2. Whereas the BIC was lowest for the two-class model, the ssaBIC continued to decrease across higher class models. In addition, the LMR test did not reach significance, thereby indicating that the one-class model best fits the data. Finally, the bootstrapped likelihood ratio test (BLRT) no longer reached significance from the 4-class model onwards, suggesting that the 3-class model best fits the data. Since simulation studies have demonstrated the superiority of (BLRT) over other parameters of fit,⁴³ we decided that the 3-class model provided the best data fit. Figure 1 shows the probability endorsement per item of the Apathy Scale for each class. The first class was particularly characterised by endorsement of mood symptoms. The second class showed high endorsement on most items of the Apathy Scale, except for items concerning external stimulation. The third class showed high endorsement on learning new things and future planning.

Table 2. Parameters of fit of Latent Class Analysis

No. of classes	Maximum likelihood	BIC	ssaBIC	BLRT	ENT	Lo-Mendell-Rubin		p-value	Proportion of individuals in class				
						2LL							
2	-930.5	2000.4	1908.7	<0.001	0.82	58.3	0.17	0.18	0.82				
3*	-909.8	2031.1	1891.9	0.02	0.89	41.4	0.3	0.17	0.07	0.76			
4	-893.7	2070.7	1884.2	0.1	0.83	32.4	0.22	0.14	0.27	0.5	0.09		
5	-879.8	2115.1	1881.1	0.4	0.87	28.5	0.22	0.2	0.14	0.07	0.25	0.34	
6	-864.7	2156.9	1875.5	0.3	0.88	29.4	0.38	0.09	0.21	0.11	0.26	0.18	0.15

Notes: BIC, Bayesian information criterion; ssaBIC, sample size adjusted Bayesian information criterion; BLRT, bootstrapped likelihood ratio test; ENT, entropy; 2LL= 2 log likelihood value

*Best-fitting model

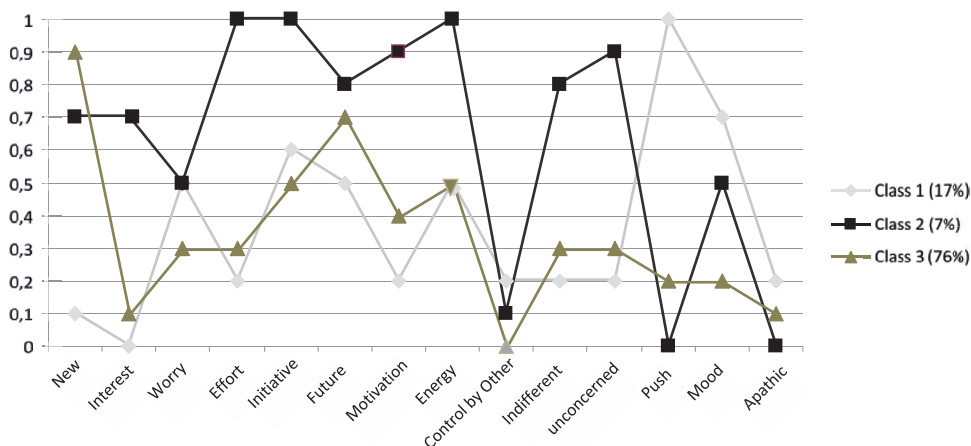


Figure 1. Probability of symptom endorsement per class – PROMODE study

Comparison between identified classes

Results of comparison of the characteristics across the three identified classes using univariate analyses are presented in Table 3. Highest scores on the Apathy Scale and the GDS were found in Class 2. Further, most persons in this Class showed high alcohol intake and lived alone, compared to the other two Classes. Lowest level of education, lowest scores on the MMSE (i.e. worst cognitive impairment), and highest scores on the Cantril's Ladder (i.e. best quality of life) were found in Class 3. No differences between the classes were found for age, gender, perceived chronic pain, the EQ-5D, the De Jong-Gierveld Loneliness questionnaire, and the HADS-A.

Finally, multivariate multinomial regression analyses, comparing class 2 and 3 with class 1 (reference), adjusted for age, gender and other putative confounders, showed that, for persons allocated to class 3, lower education (OR 0.2; 95% CI 0.03-0.8; Wald 5.3; p 0.02) and, for persons allocated to class 2, higher scores on the Apathy Scale (OR 0.3; 95% CI 0.1-0.8; Wald 5.4; p 0.02) was significantly associated with class membership, as compared with class 1. All other characteristics did not reach significance in multivariate multinomial regression analyses.

Discussion

This study, examined the presence of subtypes of apathy in general population-based older persons with apathy as assessed with the Apathy Scale using LCA and identified three classes. These three classes mainly differed in level of education, degree of hazardous alcohol intake, and severity of apathy, depression, and cognitive dysfunction. However, in multivariate multinomial regression analyses, only a lower level of education

Table 3. Distribution of characteristics across the identified latent classes (n=122)

	Class 1 (n=21, 17%)		Class2 (n=8, 7%)		Class 3 (n=93, 76%)		K-W ^a /χ ² p-value
Sociodemographic characteristics							
Age in years, mean (SD)	81	(5)	80	(4)	83	(5)	0.2
Female gender, n (%)	9	(43)	5	(63)	60	(65)	0.2
Low level of Education, n (%) ^b	3	(14)	3	(38)	52	(56)	0.002
Living alone, n (%)	11	(52)	8	(100)	61	(66)	0.054
Clinical characteristics							
Alcohol use > 14 drinks/week, n (%)	3	(14)	3	(38)	6	(7)	0.02
Chronic pain, n (%)	10	(48)	5	(63)	52	(56)	0.8
Quality of life							
Cantril's Ladder score, median (IQR)	7	(5-7)	7	(5-7)	7	(6-8)	0.05
EuroQol-5D thermometer score, median (IQR)	63	(50-75)	69	(35-78)	65	(50-80)	0.8
De Jong-Gierveld Loneliness score, median (IQR)	1	(0.5-3)	3	(1-5.8)	2	(1-3)	0.3
De Jong-Gierveld Loneliness score ≥ 2, n (%)	10	(48)	5	(63)	50	(54)	0.8
Neuropsychiatric characteristics							
Apathy Scale score, median (IQR)	16	(14.5-18)	22	(20-26)	15	(14-17)	<0.005
Geriatric Depression Scale score, median (IQR)	3	(1.5-4.5)	6	(3-8.5)	2	(1-4)	0.03
Hospital Anxiety Scale-Anxiety score, median (IQR) ^c	2	(1-4.5)	3	(0-3.8)	2	(0-4)	0.7
Mini-Mental Status Examination scale score, median IQR) ^d	29	(28-30)	27	(25-29)	26	(25-29)	0.009
<i>Notes:</i> Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.							
^a Non-parametric Kruskal-Wallis test, when count <5, Fisher's exact test was used							
^b Maximum of 6 years of schooling.							
^c Anxiety subscale of the Hospital Anxiety Depression Scale.							
^d Persons with a Mini-Mental Status Examination score < 19 were excluded.							

and severity of apathy were independent predictors for class membership, indicating that LCA, based on the Apathy Scale, merely identified classes based on different levels of apathy severity and level of education, rather than on distinct subtypes of apathy. Studies using data-driven models (such as LCA) to determine possible subtypes of apathy are lacking. The Apathy Scale itself was examined in one study investigating persons with Parkinson's disease, using factor analysis; distinct clusters of items (factors) were found, revealing a 'cognitive-behaviour' and a 'general' factor.⁴⁵ However, the aim of factor analyses is to reveal fewer underlying non-observable variables in a greater amount of observable variables, in this case all items of the Apathy Scale. Hence, this approach is 'instrument' centred, whereas LCA is a 'person-centred approach', aiming to identify groups of persons based on distinct symptom profiles, enabling further examination of associated risk factors.

Earlier studies among community-dwelling older persons and in depressed older persons, reported that a lower level of education was independently associated with apathy, except in the oldest old (mean age ≥ 80 years).^{3,21} A higher education level may protect against apathy in late life, just as it had been shown to protect against dementia,⁴⁶ perhaps because of a greater cognitive reserve⁹ or for example due to healthier lifestyle or diet, presumed to be more present among persons with higher levels of education.⁴⁷ The findings of the present study should be interpreted within the context of the following limitations and strengths. First, exclusion criteria for the original PROMODE study included current treatment for depression, and a MMSE-score < 19 or a clinical diagnosis of dementia; this could have led to selection bias excluding older persons with more severe depression and serious cognitive impairment, resulting in insufficient heterogeneity to detect distinct subtypes. Similarly, older persons with more severe apathy might not have participated in our study because of lack of motivation, resulting in inclusion of persons with only mild to moderate apathy and therefore less heterogeneity. This limits the generalizability of our results to the general population. The relatively low mean score on the Apathy Scale tends to support this idea, and therefore, findings may not be generalized to populations with higher apathy severity. Third, we had no information on neurological disorders (such as Parkinson's disease and stroke), on cardiovascular history and risk profile, objective health status and psychotropic medication use, all of which are possible predictors for class membership of apathy. Finally, since Class 2 consisted of only eight persons, the power to detect significant associations may have been too low. However, to our knowledge, this is the first study to examine apathy by LCA among general population-based older persons with apathy. Another strength of this study is the use of well-known validated measures to assess clinical characteristics, including apathy and depressive symptoms. In addition, we could use all items of the Apathy Scale for further analysis.

Conclusion

This study demonstrates that although three LCA classes of apathy emerged, these merely reflect different levels of education next to different levels of apathy severity. Therefore, in a general population-based cohort, the Apathy Scale seems to measure a relatively homogeneous construct, without indicating specific subtypes of possibly different etiology. Further research on possible subtypes of apathy is required in clinical populations, to further elucidate the position of apathy in different neuropsychiatric diseases.

References

1. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci* 1991;3:243-254.
2. Mulin E, Leone E, Dujardin K, Delliaux M, Leentjens A, Nobili F, Dessi B, Tible O, Aguera-Ortiz L, Osorio RS, Yessavage J, Dachevsky D, Verhey FR, Cruz Jentoft AJ, Blanc O, Llorca PM, Robert PH. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry* 2011;26:158-165.
3. Onyike CU, Sheppard JM, Tschanz JT, Norton MC, Green RC, Steinberg M, Welsh-Bohmer KA, Breitner JC, Lyketsos CG. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry* 2007;15:365-375.
4. Starkstein SE, Mizrahi R, Power BD. Depression in Alzheimer's disease: phenomenology, clinical correlates and treatment. *Int Rev Psychiatry* 2008;20:382-388.
5. Robert P, Onyike CU, Leentjens AF, Dujardin K, Aalten P, Starkstein S, Verhey FR, Yessavage J, Clement JP, Drapier D, Bayle F, Benoit M, Boyer P, Lorca PM, Thibaut F, Gauthier S, Grossberg G, Vellas B, Byrne J. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry* 2009;24:98-104.
6. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry* 2008;79:1088-1092.
7. Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry* 2001;158:872-877.
8. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - the Sydney Stroke Study. *Psychol Med* 2005;35:1707-1716.
9. Groeneweg-Koolhoven I, de Waal MW, van der Weele GM, Gussekloo J, van der Mast RC. Quality of life in community-dwelling older persons with apathy. *Am J Geriatr Psychiatry* 2014;22:186-194.
10. Lenze EJ, Skidmore ER, Dew MA, Butters MA, Rogers JC, Begley A, Reynolds CF, III, Munin MC. Does depression, apathy or cognitive impairment reduce the benefit of inpatient rehabilitation facilities for elderly hip fracture patients? *Gen Hosp Psychiatry* 2007;29:141-146.
11. Leontjevas R, Teerenstra S, Smalbrugge M, Vernooij-Dassen MJ, Bohlmeijer ET, Gerritsen DL, Koopmans RT. More insight into the concept of apathy: a multidisciplinary depression management program has different effects on depressive symptoms and apathy in nursing homes. *Int Psychogeriatr* 2013;25:1941-1952.
12. Resnick B, Zimmerman SI, Magaziner J, Adelman A. Use of the Apathy Evaluation Scale as a measure of motivation in elderly people. *Rehabil Nurs* 1998;23:141-147.
13. Santa N, Sugimori H, Kusuda K, Yamashita Y, Ibayashi S, Iida M. Apathy and functional recovery following first-ever stroke. *Int J Rehabil Res* 2008;31:321-326.

14. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2006;77:8-11.
15. Adams KB. Depressive symptoms, depletion, or developmental change? Withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *Gerontologist* 2001;41:768-777.
16. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int Psychogeriatr* 2010;22:426-436.
17. Eurelings LS, Ligthart SA, van Dalen JW, Moll van Charante EP, van Gool WA, Richard E. Apathy is an independent risk factor for incident cardiovascular disease in the older individual: a population-based cohort study. *Int J Geriatr Psychiatry* 2014;29:454-463.
18. Maas DW, van der Mast RC, de Craen AJ. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry* 2009;24:1177-1184.
19. Mehta M, Whyte E, Lenze E, Hardy S, Roumani Y, Subashan P, Huang W, Studenski S. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *Int J Geriatr Psychiatry* 2008;23:238-243.
20. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, Breitner JC, Steffens DC, Tschanz JT. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry* 2008;23:170-177.
21. van der Mast RC, Vinkers DJ, Stek ML, Bek MC, Westendorp RG, Gussekloo J, de Craen AJ. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry* 2008;23:266-271.
22. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr* 2010;22:819-829.
23. Ligthart SA, Richard E, Franssen NL, Eurelings LS, Beem L, Eikelenboom P, van Gool WA, Moll van Charante EP. Association of Vascular Factors With Apathy in Community-Dwelling Elderly Individuals Vascular Factors and Apathy. *Arch Gen Psychiatry* 2012;69:636-642.
24. Starkstein SE, Tranel D. Neurological and psychiatric aspects of emotion. *Handb Clin Neurol* 2012;106:53-74.
25. Nandi A, Beard JR, Galea S. Epidemiologic heterogeneity of common mood and anxiety disorders over the lifecourse in the general population: a systematic review. *BMC Psychiatry* 2009;9:31.
26. van der Weele GM, de Waal MW, van den Hout WB, van der Mast RC, de Craen AJ, Assendelft WJ, Gussekloo J. Yield and costs of direct and stepped screening for depressive symptoms in subjects aged 75 years and over in general practice. *Int J Geriatr Psychiatry* 2011;26:229-238.

27. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1992;4:134-139.
28. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991;38:143-162.
29. Wancata J, Alexandrowicz R, Marquart B, Weiss M, Friedrich F. The criterion validity of the Geriatric Depression Scale: a systematic review. *Acta Psychiatr Scand* 2006;114:398-410.
30. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull* 1988;24:709-711.
31. Lyness JM, Noel TK, Cox C, King DA, Conwell Y, Caine ED. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Arch Intern Med* 1997;157:449-454.
32. Sheikh JL, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clinical Gerontology* 1986;5:165-173.
33. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52:p 69-77.
34. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-370.
35. Cockrell JR, Folstein MF. Mini-Mental State Examination (MMSE). *Psychopharmacol Bull* 1988;24:689-692.
36. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
37. Mackin RS, Ayalon L, Feliciano L, Arean PA. The sensitivity and specificity of cognitive screening instruments to detect cognitive impairment in older adults with severe psychiatric illness. *J Geriatr Psychiatry Neurol* 2010;23:94-99.
38. Cantril H. The pattern of human concern. New Brunswick, NJ: Rutgers University; 1965.
39. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095-1108.
40. Bhattacharya S, Vogel A, Hansen ML, Waldorff FB, Waldemar G. Generic and disease-specific measures of quality of life in patients with mild Alzheimer's disease. *Dement Geriatr Cogn Disord* 2010;30:327-333.
41. de Jong GJ, van TT. [A shortened scale for overall, emotional and social loneliness]. *Tijdschr Gerontol Geriatr* 2008;39:4-15.
42. van Tilburg TG, de Jong GJ. [Reference standards for the loneliness scale]. *Tijdschr Gerontol Geriatr* 1999;30:158-163.
43. Nylund K, Bellmore A, Nishina A, Graham S. Subtypes, severity, and structural stability of peer victimization: what does latent class analysis say? *Child Dev* 2007;78:1706-1722.
44. Muthén LK and Muthén BO. *Mplus Statistical Analysis with Latent Variables. User's Guide*. Los Angeles CA: Muthen&Muthen, 2007.

45. Pedersen KF, Alves G, Larsen JP, Tysnes OB, Moller SG, Bronnick K. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *Am J Geriatr Psychiatry* 2012;20:142-148.
46. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One* 2012;7:e38268.
47. Knight A, Bryan J, Murphy K. Is the Mediterranean diet a feasible approach to preserving cognitive function and reducing risk of dementia for older adults in Western countries? New insights and future directions. *Ageing Res Rev* 2016;25:85-101



Chapter 3

Presence and correlates of apathy in non-demented depressed and non-depressed older persons

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Abstract

Background and Objectives

Apathy is a behavioral syndrome that often co-occurs with depression. Nonetheless, the etiology of apathy and depression may be different. We hypothesized that apathy occurs more often in depressed compared to non-depressed older persons; and that independent correlates for apathy will be different in depressed and non-depressed older persons.

Methods

In this cross-sectional study of Netherlands Study of Depression in Older Persons (NESDO), a total of 350 depressed older persons according to the Composite International Diagnostic Interview (CIDI) and 126 non-depressed older persons, aged at least 60 years were recruited in several Medical Centres and general practices.

In both depressed and non-depressed older persons, those with and without apathy as assessed with the Apathy Scale (score ≥ 14) were compared with regard to sociodemographic, clinical, and biological characteristics.

Results

Apathy was present in 75% of the depressed and 25% of the non-depressed older persons. Independent correlates of apathy in both depressed and non-depressed older persons were male gender and less education. Furthermore, in depressed older persons, higher scores on the Inventory of Depressive Symptomatology (IDS) and, in non-depressed older persons, a higher C-reactive protein (CRP) level correlated independently with apathy.

Conclusions

Apathy occurred frequently among both depressed and non-depressed older persons. Among depressed older persons, apathy appeared to be a symptom of more serious depression, whereas among non-depressed persons apathy was associated with increased CRP being a marker for immune activation, suggesting a different etiology for apathy in its own right.

Introduction

Apathy as a distinct, clinically relevant syndrome is a well-known motivational disorder in late life, that is characterized by behavioral, cognitive and emotional symptoms interfering with adequate daily functioning.¹⁻³ It may occur in community dwelling older persons (1-27%),⁴⁻⁶ as well as in clinical populations with various neuropsychiatric disorders such as dementia,³ Parkinson's disease² and depression (42-96%),⁷⁻¹⁰ then being a very prominent feature of that disorder.^{1-3,11,12} Apathy as a distinct clinical syndrome may persist over time and is associated with poor functional outcome, reduced quality of life,¹³ poor prognosis and increased overall mortality rates.^{14,15}

Little is known about apathy in depressive disorders at old age, since most studies till now examined apathy especially in clinical populations suffering from dementia, stroke and Parkinson's disease, with and without comorbid depressive symptoms.^{11,16-18} Although depression and apathy often co-occur, increasing evidence shows that apathy may be a distinct, clinically relevant syndrome with etiologies possibly different from depression. Recent literature showed that among community-dwelling older persons free from depressive and apathy symptoms at base-line, higher C-reactive protein (CRP) concentrations predicted an increase in depressive symptoms but not apathy,⁵ whereas cardiovascular disease and cardiovascular risk factors predicted the occurrence of apathy, but not depressive symptoms.^{19,20} Also, MRI studies of the brain showed that depression and apathy at old age were both associated with reduced gray matter volumes, but in different areas of the brain.¹²

Further, in 1889 community-based non-depressed older persons without stroke or other cardiovascular disease, increased CRP concentration, assessed as one of the cardiovascular risk factors, was cross-sectionally associated with a higher apathy score.²⁰ Conversely, in 377 community-based older persons (≥ 85 years), CRP was cross-sectionally nor longitudinally associated with presence of apathy.⁵ Thus, the relation between CRP concentration as a marker for immune activation and apathy remains unclear.

To gain more insight into the characteristics of apathy among depressed and non-depressed older persons, this cross-sectional study aimed at investigating the presence and various correlates of apathy as a syndrome in its own right. We hypothesized that apathy occurs more often in depressed older persons and has different independent correlates for apathy than in non-depressed older persons.

We assumed that in depressed older persons apathy would correlate with severity of depression and in non-depressed older persons, based on the literature, with cognitive impairment, vascular disease, frailty and immune activation.

Methods

Study design

This cross-sectional study is part of the Netherlands Study of Depression in Older persons (NESDO), a multi-site naturalistic, 6-years prospective cohort study that was designed to examine various determinants, course and consequences of depressive disorders in older persons (≥ 60 years). The full design of this study is described in an earlier report.²¹

Between 2007 and 2010, a total of 378 depressed older persons with a primary diagnosis of major depression, dysthymia or minor depression in the previous 6 months according to DSM-IV criteria (American Psychiatric association) as assessed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1; life-time version)²² were recruited in university medical centers, mental health care institutes and general practitioners. Furthermore a total of 132 control older persons without a life-time diagnosis of depression were recruited from 14 general practices. Exclusion criteria were: a diagnosis of dementia or a Mini-Mental State Examination-score (MMSE) under 18; presence of a psychotic disorder; and insufficient mastery of the Dutch language.

The study protocol of the NESDO study has been approved by the Ethical Review boards of all participating centers. Before enrollment all participants gave verbal and written informed consent. For this sub-study, only persons with complete Apathy Scale-scores were included resulting in data of 350 depressed and 126 non-depressed older persons for further analyses (see Figure 1).

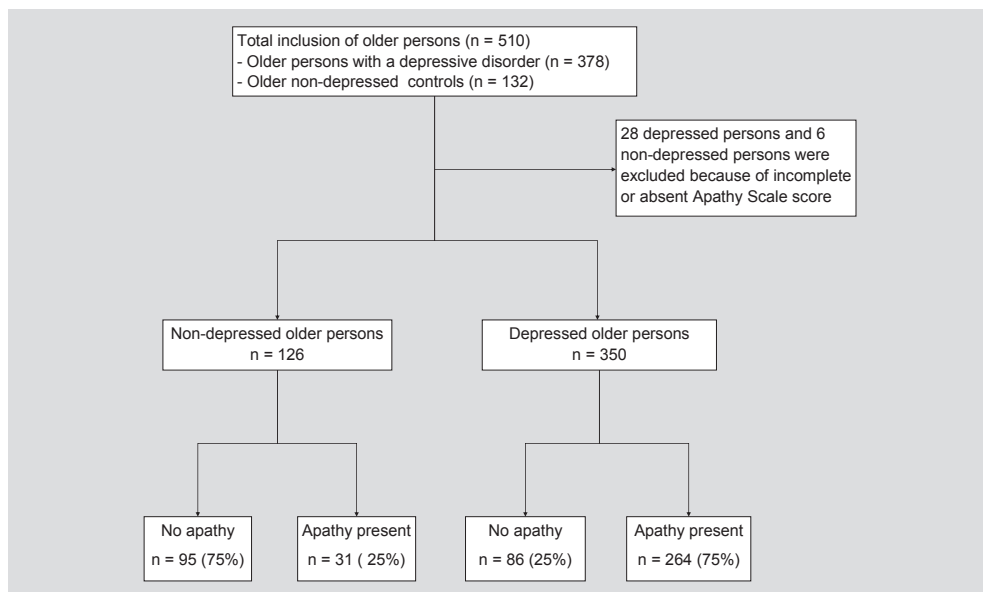


Figure 1. Flow chart included persons

Measures

Assessment of apathy

Apathy was assessed with the Apathy Scale used as a self-report questionnaire.^{23,24} The Apathy Scale is an abbreviation of the Apathy Evaluation Scale showing a good one-week test-retest ($r=.90$) and inter-rater ($r=.81$) reliability and internal validity in both self-reported and observer-rated measurements.^{23,24} The Apathy Scale consists of 14 items with four possible answers ranging from 0-3 points, with higher scores indicating more severe apathy.²³ A score ≥ 14 points is indicative for the presence of clinically relevant apathy.^{23,25}

Assessment of depression and cognition

Severity of depression was assessed using the 30-item self-report Inventory of Depressive Symptomatology (IDS-SR),²⁶ with higher scores indicating more severe depression. Information on global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE).²⁷

Assessment sociodemographic, clinical and biological characteristics

For all persons the sociodemographic characteristics including age, sex, education and living situation were obtained. The following clinical characteristics were assessed; the presence of chronic diseases, presence and severity of pain and use of medication. For assessment of chronic diseases, a self-rating questionnaire was used, that was shown to be independent of cognitive impairment or depressive symptomatology.²⁸ Presence of cardiovascular disease comprised cardiac disease, peripheral atherosclerosis and/or stroke. Pain experience was assessed with the 10 items of the self-report Chronic Graded Pain Scale (CGPS).²⁹ Medication use was determined by assessing the medication that the participants brought with them,²¹ and classified using the Anatomical Therapeutic Chemical (ATC) Classification System.³⁰ Biological markers of immune function (Interleukin 6 and C-reactive protein levels) and nutritional status (albumin concentration) were assessed in fasting blood. Further, walking speed as a measure for frailty was determined by measuring the time in seconds needed to complete a six meter walk.³¹

Statistical analyses

All data are presented as numbers with percentages, medians with interquartile ranges (IQR) or means with standard deviations (SD) where appropriate. For group comparisons on apathy correlates, the Mann-Whitney U for continuous data was used, because of a non-parametric distribution, and χ^2 tests were used for categorical data. Fisher's exact test was used when frequencies were lower than five in one or more cells.

Since values of CRP, IL6 and walking speed showed a skewed distribution, these were $\log_e$ -transformed. Multivariate regression analyses investigating independent correlates

of apathy were done separately in the groups of depressed and non-depressed older persons, entering variables that showed a significance level of <0.1 in the univariate analyses, next to age and gender that were forced into the multivariate models. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 20.0 for Windows (IBM).

Results

Depressed ($n=350$) and non-depressed ($n=126$) older persons showed no significant difference in age (70 ± 7 and 71 ± 7 years, respectively) and gender distribution (62% and 66% female gender, respectively) (data not shown). Apathy, as defined by a score ≥ 14 on the Apathy Scale, was present in 75% ($n=264$) of the depressed older persons and in 25% ($n=31$) of the non-depressed older persons.

Table 1 shows the characteristics of depressed older persons with apathy compared to those without apathy. Apathy was associated with male gender and having had fewer years of education. Furthermore, IDS scores were significantly higher and walking speed slower in depressed older persons with apathy, compared to those without apathy.

Among non-depressed older persons, apathy was associated with higher age, fewer years of education and, additionally, with having less often a current partner (table 2). Furthermore, non-depressed older persons with apathy more often had cardiovascular diseases, used more psychotropic and analgesic medication, and had higher scores on the IDS and lower scores on the MMSE compared to non-depressed older persons without apathy. In addition, apathy was associated with significantly higher levels of CRP and IL6 and slower walking speed.

Table 3 and 4 show the independent correlates of apathy among both the depressed and non-depressed older persons. Independent correlates for apathy among depressed older persons were male gender, less education, and higher IDS scores. In addition, among non-depressed older persons, apathy was independently correlated to increased CRP level.

For sensitivity analysis, all multivariate analyses were repeated using cut-off scores of 13 and 15 on the Apathy Scale, respectively, which yielded similar results. Additionally, we analysed the correlation between the total Apathy Scale and IDS scores ($r=0.3$), showing a 10 per cent shared variance only.

Table 1. Characteristics of depressed older persons with and without apathy (n=350)

	Apathy absent (n=86, 25%)		Apathy present (n=264, 75%)		fd (F)	P ^a
Sociodemographic characteristics						
Age in years, mean (SD)	70	(8)	71	(7)	348 (0.7)	0.2
Female gender	65	(76)	166	(63)	1	0.04
Education in years	10	(9-15)	10	(9-11)		0.03
Current partner	46	(54)	139	(53)	1	0.99
Clinical characteristics						
<i>Presence of chronic disease^b</i>	26	(30)	101	(38)	1	0.2
Cardiovascular disease ^c	27	(31)	95	(36)	1	0.5
Diabetes Mellitus	8	(9)	34	(13)	1	0.5
Arthritis/rheuma	39	(45)	144	(55)	1	0.2
Chronic lung disease	11	(13)	42	(16)	1	0.6
<i>Presence of pain^d</i>						
Intensity	40	(26-61)	50	(33-63)		0.09
Disability	25	(0-53)	32	(3-63)		0.1
<i>Medication use</i>	84	(98)	261	(99)	1	0.8
Psychotropic medication ^e	66	(77)	215	(81)	1	0.2
Benzodiazepines	27	(31)	109	(41)	1	0.3
Antidepressants	58	(67)	197	(75)	1	0.2
Antipsychotics	10	(12)	38	(14)	1	0.5
Analgesic medication ^f	24	(28)	90	(33)	1	0.4
Neuropsychiatric characteristics						
IDS score	22	(15-31)	31	(22-41)		<0.005
AS score	10	(8-12)	19	(17-22)		<0.005
MMSE score ^g	28	(27-29)	28	(27-29)		0.3
Biological characteristics						
Albumine (g/l)	42	(40-44)	42	(40-45)		0.6
IL6 (pg/ml) ^h	0.8	(0.6-1)	0.8	(0.7-1)	340 (0.01)	0.5
CRP (mg/l) ^h	1.7	(1.3-2.2)	2.1	(1.8-2.4)	336 (0.6)	0.3
Walking speed (sec.) ^h	6.4	(5.9-7)	7.1	(6.7-7.4)	344 (0.3)	0.03

Notes: Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.

IDS: Inventory of Depressive Symptomatology, 30-items self-rating ; AS: Apathy Scale, 14-items self-rating; MMSE: Mini-Mental State Examination; IL6: Interleukin-6; CRP: C-reactive protein

^a P-values by chi-square, t-test or Mann-Whitney where appropriate; when count <5, Fisher's exact test was used;

^b Presence of chronic disease is defined by the median cut-off score of numbers of chronic diseases;

^c Included coronar, vascular and cerebral;

^d Pain intensity and disability scores as assessed with the Chronic Graded Pain Scale with scores 0-100 and higher scores indicating more intense or disabling pain;

^e Psychotropic medication includes the use of benzodiazepines, antidepressants and antipsychotic drugs;

^f Analgesic includes the use of peripheral working analgesic medication, NSAID's and analid;

^g Subjects with Mini-Mental Status Examination < 19 were excluded;

^h Geometric mean and 95% CI.

Table 2. Characteristics of non-depressed older persons with and without apathy (n=126)

	Apathy absent (n=95, 75%)		Apathy present (n=31, 25%)		Fd (F)	P ^a
Sociodemographic characteristics						
Age in years, mean (SD)	69	(6)	73	(8)	42 (6.1)	0.03
Female gender	62	(65)	16	(52)	1	0.3
Education in years	12	(10-15)	11	(9-12)		0.001
Current partner	77	(81)	19	(61)	1	0.045
Clinical characteristics						
<i>Presence of Chronic disease present^b</i>	41	(43)	13	(42)	1	1
Cardiovascular disease ^c	17	(18)	13	(42)	1	0.01
Diabetes Mellitus	11	(12)	5	(16)	1	0.7
Arthritis/rheuma	44	(46)	16	(52)	1	0.8
Chronic lung disease	8	(8)	1	(3)	1	0.6
<i>Pain^d</i>						
Intensity	30	(0-43)	30	(10-53)		0.4
Disability	0	(0-20)	0	(0-37)		0.9
<i>Medication use</i>	79	(83)	28	(90)	1	0.5
Psychotropic medication ^e	1	(1)	4	(13)	1	<0.005
Benzodiazepines	1	(1)	2	(6)	1	0.3
Antidepressants	0	(0)	2	(6)	1	0.06
Antipsychotics	0	(0)	0	(0)	1	-
Analgesic medication ^f	14	(15)	11	(36)	1	0.02
Neuropsychiatric characteristics						
IDS score	6	(4-9)	7	(5-12)		0.04
AS score	9	(6-11)	16	(14-17)		<0.005
MMSE score ^g	29	(28-30)	28	(27-29)		0.04
Biological characteristics						
Albumin (g/l)	42	(40-45)	43	(41-46)		0.3
IL6 (pg/ml) ^h	0.7	(0.6-0.9)	1.1	(0.8-1.6)	121 (1.2)	0.049
CRP (mg/l) ^h	1.4	(1.1-1.7)	2.8	(1.96-3.9)	119 (0.1)	<0.005
Walking speed (sec.) ^h	6	(5.6-6.4)	6.8	(6-7.6)	123 (0.4)	0.03

Notes: Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.

IDS: Inventory of Depressive Symptomatology, 30-items self-rating ; AS: Apathy Scale, 14-items self-rating; MMSE: Mini-Mental State Examination; IL6: Interleukin-6; CRP: C-reactive protein

^a P-values by chi-square, t-test or Mann-Whitney where appropriate; when count <5, Fisher's exact test was used;

^b Presence of chronic disease is defined by the median cut-off score of numbers of chronic diseases;

^c Included coronar, vascular and cerebral;

^d Pain intensity and disability scores as assessed with the Chronic Graded Pain Scale with scores 0-100 and higher scores indicating more intense or disabling pain;

^e Psychotropic medication includes the use of benzodiazepines, antidepressants and antipsychotic drugs;

^f Analgesic includes the use of peripheral working analgesic medication, NSAID's and analid;

^g Subjects with Mini-Mental Status Examination < 19 were excluded;

^h Geometric mean and 95% CI.

Table 3. Independent correlates of apathy in depressed older persons (n=350)

	Multivariate analyses			
	OR	95%CI	Wald	P
Age in years	1.0	0.99-1.1	2.3	0.1
Female gender	0.4	0.2-0.7	8.8	<0.005
Education in years	0.9	0.8-0.99	5.0	0.03
Pain intensity	0.99	0.98-1.0	0.7	0.4
IDS	1.1	1.0-1.1	22.2	<0.005
Log _e walking speed (sec.)	1.3	0.5-2.95	0.3	0.6

Notes: Multivariate analyses using variables that showed a significance level of $p < 0.1$ on the univariate analyses
IDS: : Inventory of Depressive Symptomatology, 30-items self-rating

Table 4. Independent correlates of apathy in non-depressed older persons (n=126)

	Multivariate analyses			
	OR	95%CI	Wald	P
Age in years	1.03	0.95-1.1	0.5	0.5
Female gender	0.2	0.08-0.8	5.4	0.02
Education in years	0.8	0.7-0.9	6.9	0.008
Current partner	1.8	0.5-6.9	0.7	0.4
Cardiovascular disease present	1.3	0.4-4.6	0.2	0.7
Use of analgesic medication	1.8	0.5-6.8	0.8	0.4
IDS	1.1	0.96-1.2	1.6	0.2
MMSE	0.96	0.7-1.4	0.06	0.8
Log _e CRP (mg/l)	1.8	1.0-3.1	4.1	0.04
Log _e IL6 (pg/ml)	0.8	0.3-2.2	0.2	0.6
Log _e walking speed (sec.)	1.1	0.1-7.8	0.004	0.9

Notes: Multivariate analyses using variables that showed a significance level of $p < 0.1$ on the univariate analyses
IDS: Inventory of Depressive Symptomatology, 30-items self-rating; MMSE: Mini- Mental State Examination; IL6: Interleukin-6; CRP: C-reactive protein

Discussion

Clinically relevant apathy was present in 75% of the depressed and 25 % of the non-depressed older persons. In both depressed and non-depressed older persons, apathy was associated with male gender and less education. Additionally, apathy was strongly associated with the severity of depression in depressed persons and with a higher CRP level in non-depressed persons.

An occurrence of 75% for apathy, as was found in the depressed older persons is within the wide range of 42-96%, reported in earlier studies.^{8,9,32} Also, the 11-27% occurrence

of apathy among non-depressed older persons is in line with most community studies,^{13,19,20,33} although some studies reported lower percentages.⁴ Our relatively high occurrence rate of apathy in both groups depressed and non-depressed persons may be due to the use of the self-administered method to assess apathy. This may have led to higher scores, compared to observer-rated scores as was found in a study on self-report of the 15-item version of the Geriatric Depression Scale.³⁴ Sensitive questions may be answered more truthfully when self-administered, since the interviewer's influence to give social desirable answers is absent. On the other hand, explanation of the items by an interviewer can solve misunderstandings, leading to more specific answers.³⁴

In the depressed older group, presence of apathy was particularly associated with severity of depression, suggesting that the symptom apathy indicates more severe depression, which has been found in many studies before.^{8,16,32,35} Also, apathy as a syndrome in its own right may be distinguished from depression by the absence of mood-related symptoms.^{36,37} Further, different etiologies for apathy as a distinct syndrome and late-life depression have been found among older persons.^{5,19,20,38} Also, the treatment of apathy differs from depression in that antidepressants will treat depression but not always apathy.^{9,39} So, it remains debatable whether apathy in depression can be regarded as a distinct behavioral syndrome.

Among non-depressed older persons, CRP was one of the independent correlates of apathy, which corresponds with the results of a large community-based, cross-sectional study among 3534 older persons aged 70-79 years;²⁰ but contrasts with the findings in the community-based, longitudinal Leiden 85-Plus Study among 460 older persons (≥ 85 year).⁵ Our results may be different from the latter due to our population being younger, the use of the well-validated Apathy Scale, and considering continuous CRP values instead of tertiles.^{5,20}

Male gender was independently correlated to apathy in both the depressed and non-depressed older persons, which has been reported previously only among non-depressed community-based older persons (mean age 69.9 years),⁶ although not consistently.³³ Also, less education as independent correlate of apathy has been reported before in several studies among community-dwelling older persons.^{4,19} Possibly, having had more education protects not only against dementia,⁴⁰ but also against apathy in late life, as a result of greater cognitive reserve.

Depression and apathy were diagnosed using well known validated measures which are an important strength of our study, whereas presence and similar characteristics of apathy in a large group of depressed and non-depressed general-based older persons were investigated. However, an important limitation of our study is the cross-sectional design which prevents drawing causal inferences. Furthermore, our population was relatively young and, therefore, our results cannot be generalized to older old persons. We are also aware of the fact that a conceptual problem is present, since depression and apathy symptoms overlap, especially with regard to motivational symptoms, but

in our study the overlap of the Apathy Scale and IDS was very low. Finally, although we included both mildly and severely depressed older persons selection bias may have occurred, since older persons with most severe depression and apathy were not able to participate in the study.

In conclusion, this study showed that apathy occurred frequently among both depressed and non-depressed older persons. Among depressed older persons, apathy appeared to be a symptom of more serious depression, whereas among non-depressed persons apathy was associated with increased CRP, a marker for inflammation, suggesting a different etiology for apathy as a syndrome in its own right. Importantly, information about apathy and its possible concomitants may result in a better understanding and treatment of apathy.

References

1. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci* 1991;3:243-254.
2. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry* 2008;79:1088-1092.
3. Robert P, Onyike CU, Leentjens AF et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry* 2009;24:98-104.
4. Onyike CU, Sheppard JM, Tschanz JT et al. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry* 2007;15:365-375.
5. Maas DW, van der Mast RC, de Craen AJ. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry* 2009;24:1177-1184.
6. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int Psychogeriatr* 2010;22:426-436.
7. Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 2000;157:708-714.
8. Lampe IK, Heeren TJ. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *Int Psychogeriatr* 2004;16:481-486.
9. Wongpakaran N, van RR, Wongpakaran T, Clarke D. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Ann Gen Psychiatry* 2007;6:7.
10. Mulin E, Leone E, Dujardin K et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry* 2011;26:158-165.
11. Levy ML, Cummings JL, Fairbanks LA et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci* 1998;10:314-319.
12. Lavretsky H, Ballmaier M, Pham D, Toga A, Kumar A. Neuroanatomical characteristics of geriatric apathy and depression: a magnetic resonance imaging study. *Am J Geriatr Psychiatry* 2007;15:386-394.
13. Groeneweg-Koolhoven I, de Waal MW, van der Weele GM, Gussekloo J, van der Mast RC. Quality of life in community-dwelling older persons with apathy. *Am J Geriatr Psychiatry* 2014;22:186-194.
14. Vinkers DJ, Stek ML, Gussekloo J, van der Mast RC, Westendorp RG. Does depression in old age increase only cardiovascular mortality? The Leiden 85-plus Study. *Int J Geriatr Psychiatry* 2004;19:852-857.
15. Lavretsky H, Zheng L, Weiner MW et al. Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. *Am J Psychiatry* 2010;167:589-597.

16. Starkstein SE, Petracca G, Chmerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry* 2001;158:872-877.
17. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002;288:1475-1483.
18. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - the Sydney Stroke Study. *Psychol Med* 2005;35:1707-1716.
19. van der Mast RC, Vinkers DJ, Stek ML et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry* 2008;23:266-271.
20. Ligthart SA, Richard E, Fransen NL et al. Association of Vascular Factors With Apathy in Community-Dwelling Elderly Individuals Vascular Factors and Apathy. *Arch Gen Psychiatry* 2012;69:636-642.
21. Comijs HC, van Marwijk HW, van der Mast RC et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res Notes* 2011;4:524.
22. Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *Br J Psychiatry* 1991;159:645-53, 658.
23. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1992;4:134-139.
24. Pedersen KF, Alves G, Larsen JP, Tysnes OB, Moller SG, Bronnick K. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *Am J Geriatr Psychiatry* 2012;20:142-148.
25. van Reekum R., Stuss DT, Ostrander L. Apathy: why care? *J Neuropsychiatry Clin Neurosci* 2005;17:7-19.
26. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* 1996;26:477-486.
27. Mackin RS, Ayalon L, Feliciano L, Arean PA. The sensitivity and specificity of cognitive screening instruments to detect cognitive impairment in older adults with severe psychiatric illness. *J Geriatr Psychiatry Neurol* 2010;23:94-99.
28. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol* 1996;49:1407-1417.
29. Von KM, Miglioretti DL. A prognostic approach to defining chronic pain. *Pain* 2005;117:304-313.

30. Norwegian Institute of public health. Anatomical Therapeutic Chemical Classification with used daydoses. WHO Collaborating Centre for Drug Statistics, 2011 http://www.whocc.no/atc_ddd_index/.
31. Guralnik JM, Ferrucci L, Pieper CF et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci* 2000;55:M221-M231.
32. Marin RS, Firinciogullari S, Biedrzycki RC. Group differences in the relationship between apathy and depression. *J Nerv Ment Dis* 1994;182:235-239.
33. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr* 2010;22:819-829.
34. de Waal MW, van der Weele GM, van der Mast RC, Assendelft WJ, Gussekloo J. The influence of the administration method on scores of the 15-item Geriatric Depression Scale in old age. *Psychiatry Res* 2012;197:280-284.
35. Mehta M, Whyte E, Lenze E et al. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *Int J Geriatr Psychiatry* 2008;23:238-243.
36. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord* 1993;28:117-124.
37. Leontjevas R, van HS, Waterink W, Mulders A. Apathy and depressive mood in nursing home patients with early-onset dementia. *Am J Alzheimers Dis Other Dement* 2009;24:341-348.
38. Yuen GS, Bhutani S, Lucas BJ et al. Apathy in Late-Life Depression: Common, Persistent, and Disabling. *Am J Geriatr Psychiatry* 2015;23:488-494.
39. Yuen GS, Gunning FM, Woods E, Klimstra SA, Hoptman MJ, Alexopoulos GS. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *J Affect Disord* 2014;166:179-186.
40. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One* 2012;7:e38268.



Chapter 4

Apathy in older persons with depression: course and predictors: The NESDO study

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Abstract

Objectives

Apathy is a common behavioral syndrome, influencing different areas of daily functioning and often seen in depression. Little is known about the course of apathy in depression. In this study we examine the course and predicting factors of apathy in older persons with depression.

Method

Data of 266 older persons with depression participating in the Netherlands Study of Depression in Older Persons (NESDO), all aged at least 60 years with complete Apathy Scale scores at baseline and 2-year follow-up, were included in this study. Associations between several baseline variables and severity, incidence and persistence of apathy were examined using regression analyses.

Results

At 2-year follow-up, the severity of apathy was predicted by the severity of apathy at baseline and incidence rate of apathy was 36%, with a lower baseline Mini-Mental Status Examination score being an independent predictor. Older persons with incident apathy did not differ in remission rate of depression compared to those without apathy at follow-up. Persistence rate of apathy was 80% and was independently predicted by a higher baseline Apathy Scale score and, surprisingly, by less use of benzodiazepines. Persons with persistent apathy were less likely to recover from depression than those who remitted from apathy.

Conclusion

Severity of apathy at baseline, but not depression, predicted apathy at follow-up. Incident apathy was predicted by poorer cognitive function, whereas severe apathy at baseline predicted its persistence. Remarkably, new apathy was not associated with worse outcome of depression whereas persistent apathy was.

Introduction

Apathy was originally considered to be a symptom of depression referring to a lack of interest or emotion.¹ However, it is increasingly recognized as a distinct behavioral syndrome characterized by the core symptom of decreased or absent motivation or drive and a set of specific clinical (behavioral, cognitive and emotional) symptoms.^{2,3} Apathy is found in many late-life neuropsychiatric disorders such as dementia, Parkinson's disease and in depression.^{1,2,4} The presence of apathy is important since it is associated with poor functional outcome, reduced quality of life, worse prognosis and increased mortality.⁵⁻⁷ In patients with depression, apathy is a predictor of poor response to antidepressants⁸ and chronicity of depression⁹ and is more often associated with disability than other depressive symptoms.¹⁰

It remains debatable whether apathy can be regarded as a distinct behavioral syndrome apart from depression. Although apathy may be distinguished from depression by the absence of mood-related symptoms, there is considerable overlap with depression with regard to motivational symptoms.^{11,12} In addition, different etiologies for apathy and for late-life depression have been found among older persons, supporting the notion that, in this group, apathy can be considered a distinct behavioral syndrome apart from depression.¹³⁻¹⁷ It is also reported that treatment of apathy differs from depression in that antidepressants will treat depression but will not always treat apathy.^{9,10,18} It is suggested that apathy could be a residual symptom of depression, or is caused by antidepressant medication, especially Selective Serotonin Reuptake Inhibitors (SSRIs).^{19,20} However, large epidemiologic studies examining the course and predictors of apathy in older population with depression are lacking.

With the aim to elucidate the underlying characteristics of apathy in late-life depression, this study investigates the incidence and course of apathy in a group of older persons with depression and examines whether sociodemographic, clinical, and biological variables predicted the severity, incidence, and persistence of apathy at 2-year follow-up.

We hypothesized that older persons with depression having clinically relevant apathy at baseline will show poorer recovery from depression and persistence of apathy at follow-up. Further, we hypothesized that older persons having more severe depression at baseline will more often show clinically relevant apathy at follow-up.

Methods

Study design

This longitudinal study is part of the Netherlands Study of Depression in Older persons (NESDO), a multicenter naturalistic prospective cohort study designed to examine the neurobiological, psychosocial and physical determinants; course; and consequences of

depressive disorders in older persons (≥ 60 years) over a period of 6 years. The full design of this study is described in an earlier report.²¹

In total, 378 persons with depression having a primary diagnosis of major depression, dysthymia or minor depression in the past 6 months according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, Text Revision; DSM-IV-TR) criteria as assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization version 2.1; life-time version), were recruited from mental health-care institutions and general practices.

Exclusion criteria included a clinical diagnosis of dementia or a Mini-Mental State Examination (MMSE) score ≤ 18 , presence of a psychotic disorder, and insufficient mastery of the Dutch language. The study protocol of the NESDO study was approved by the ethical review boards of all participating centers. Before enrollment, all participants gave verbal and written informed consent.

Of the 378 eligible participants with a depressive disorder at baseline, a second face-to-face assessment was performed in 285 of these persons at 2-year follow-up. Of the 93 persons who dropped out, 26 (28%) were deceased, 47 (51%) were physically or mentally unable to participate, and 20 (22%) had no time/interest to participate in the second face-to-face interview.²²

In the present study, only persons with complete Apathy Scale scores at baseline and at 2-year follow-up are included, resulting in data of 266 persons (of the 285 responders with depression) available for the analyses (Figure 1).

Measures

Assessment of Apathy

Clinically relevant apathy was assessed with the Apathy Scale, an abbreviated version of the Apathy Evaluation Scale,²³ used as a self-report questionnaire.^{24,25} The Apathy Scale consists of 14 items, each with 4 possible answers ranging from 0 to 3 points^{24,25} (total maximum of 42 points), with higher scores indicating more severe apathy.²⁴ In different clinical populations, a cut-off score of 14 showed a moderate sensitivity and a high specificity for the presence of clinically relevant apathy.²⁴⁻²⁷

Assessment of Depressive Symptoms and Cognitive Function

To determine the current diagnosis of major depression, dysthymia or minor depression (past month) at follow-up, the DSM-IV-TR criteria (as assessed with the CIDI) were used. Severity of depression was assessed with the 30-item self-report Inventory of Depressive Symptomatology (IDS-SR), with higher scores indicating more severe depression.²⁸ Global cognitive functioning and executive functioning were assessed with the MMSE^{29,30} and the Stroop color-word test, respectively.³¹

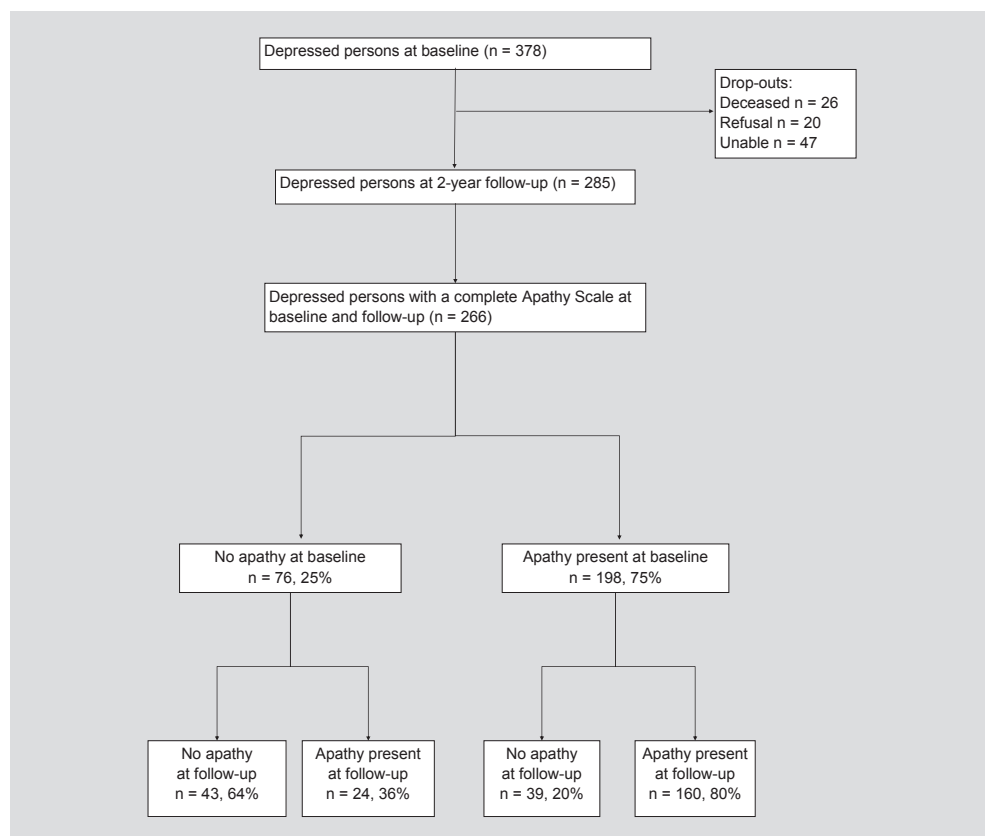


Figure 1. Flow chart research population (n=266)

Assessment of Sociodemographic, Clinical and Biological Characteristics

Sociodemographic information on age, sex, education, living situation and use of medication was collected. Clinical information on the total number of chronic diseases including the presence of cardiovascular diseases (cardiac diseases, cerebrovascular accidents, peripheral atherosclerosis taken together), hypertension, diabetes mellitus, chronic non-specific lung diseases, liver diseases, thyroid diseases, epilepsy, intestinal diseases, arthritis/ arthrosis, and cancer was obtained using a self-rating questionnaire.^{21,32} The accuracy of self-reports of these diseases compared to general practitioner information is considered adequate and independent of cognitive impairment or depressive symptomatology.³³ Psychotropic medication use was classified with the Anatomical Therapeutic Chemical Classification System.³⁴ Further, walking speed as a measure for frailty was determined by measuring the time in seconds needed to complete a six-meter walk.³⁵ Energy expenditure based on sports and daily activities was calculated with the International Physical Activities Questionnaire (IPAQ) and presented in metabolic equivalent (MET) minutes.³⁶ Cardiovascular risk was

computed using the cardiovascular disease risk function, derived from the Dubbo study also containing Framingham items, which assessed the incidence of cardiovascular disease among older persons (≥ 60 years); this provides a good prediction score for cardiovascular disease risk and is not limited to age, as is the Framingham score (30-75 years).³⁷

Statistical analysis

Data are presented as numbers with percentages, medians with interquartile ranges (IQR), or means with standard deviations (SD), where appropriate. Linear logistic regression analysis was used to investigate the association between the baseline variables and severity of apathy at follow-up.

To determine the predictive variables for incident and persistent apathy in older persons with depression, univariate and multivariate logistic regression analyses were performed with the presence or absence of apathy at 2-year follow-up as the dependent variable, and the baseline characteristics as the independent variables. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed. A p -value < 0.05 was considered statistically significant. In the multivariate logistic regression analyses, all variables from the univariate analysis with $p < 0.10$ and age and sex were entered in the model.

For sensitivity analysis, all univariate and multivariate analyses were repeated using cut-off scores of 13, 15 and 18 on the Apathy Scale.³⁸

Statistical analyses were performed with SPSS 22.0 (IBM for Windows).

Results

Non-response analyses showed that compared to the 266 study participants, persons lost to follow-up did not differ at baseline with regard to age, sex, having a partner, educational level, number of chronic diseases, or scores on the MMSE, the Apathy Scale and the IDS.

Using linear regression analysis the following baseline variables were associated with the continuous Apathy Scale scores at follow-up (Table 1): age, total number of chronic diseases, cardiovascular disease, number of medications, use of analgesics, IDS score, Apathy Scale score, presence of clinically relevant apathy, cardiovascular risk, walking speed, and IPAQ. Only the Apathy Scale score at baseline was independently associated with the Apathy Scale scores at follow-up.

Of the 67 older persons with depression without apathy at baseline, 24 (36%) had incident apathy at 2-year follow-up, whereas 33 (49%) had neither apathy nor depression at follow-up (Figure 2). Compared to those who showed no apathy at follow-up, older persons with incident apathy did not differ with regard to remission of depression (77% versus 71%).

Table 1. Univariate linear relationship between sociodemographic and clinical characteristics at baseline and total Apathy Scale scores at follow-up of older persons with depression (n=266)

	B	SE	Beta	p
Sociodemographic characteristics				
Age	0.1	0.06	0.1	0.04
Female gender	-0.7	0.9	-0.5	0.4
Education	-0.2	0.1	-0.1	0.08
Current partner	0.4	0.8	0.03	0.6
Clinical characteristics				
<i>Total chronic disease</i>	0.6	0.3	0.1	0.02
Cardiovascular disease ^a	1.6	0.9	0.1	0.07
Diabetes mellitus	2.0	1.2	0.099	0.1
<i>Number of medications used</i>	0.3	0.1	0.1	0.03
Psychotropic medication ^b	1.5	1.2	0.07	0.2
Analgesic medication ^c	1.8	0.9	0.1	0.04
Benzodiazepine	-0.8	0.8	-0.06	0.4
Antipsychotics	0.5	1.3	0.03	0.7
Antidepressives	0.7	0.9	0.05	0.5
Neuropsychiatric characteristics				
IDS score	0.1	0.03	0.33	<0.005
AS score	0.7	0.06	0.6	<0.005
Apathy present at base-line	6.3	0.9	0.4	<0.005
MMSE score ^d	-0.3	0.2	-0.07	0.2
STROOP score	0.2	0.4	0.03	0.6
Biological characteristics				
Cardiovascular risk ^e	0.1	0.06	0.1	0.03
Walking speed (sec) ^f	3.6	1.0	0.2	<0.005
Glucose ^f	-0.4	2.3	-0.01	0.9
Body mass index	0.1	0.1	0.08	0.2
IPAQ (MET minutes) ^f	-0.9	0.5	-0.1	0.05
Depression present at follow-up	4.6	0.8	0.3	<0.005

Notes: Abbreviations: AS, Apathy Scale, 14-item self-rating; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; IDS, Inventory of Depressive Symptomatology, 30-item self-rating; IPAQ, International Physical Activities Questionnaire in MET minutes; MET, metabolic equivalent; MMSE, Mini-Mental State Examination; NSAID, nonsteroidal anti-inflammatory drug; SE, standard error; syst. BP, systolic blood pressure.

^a Including heart disease, vascular disease, and stroke;

^b Psychotropic medication includes the use of benzodiazepines, antidepressants, and antipsychotic drugs;

^c Analgesic includes the use of peripheral working analgesic medication, NSAIDs and analid;

^d Participants with MMSE < 19 were excluded;

^e Computed with: $CVD = 1/(1 + e^{-k})$ with $k = -8.65 + 0.057 \times \text{age} - 0.61 \times \text{gender} + 0.749 \times \text{antihypertensive medication} + 0.008 \times \text{syst. BP} + 0.458 \times \text{smoking} + 0.18 \times \text{cholesterol} - 0.234 \times \text{HDL cholesterol} + 0.857 \times \text{DM}$;

^f Geometric mean and 95% CI

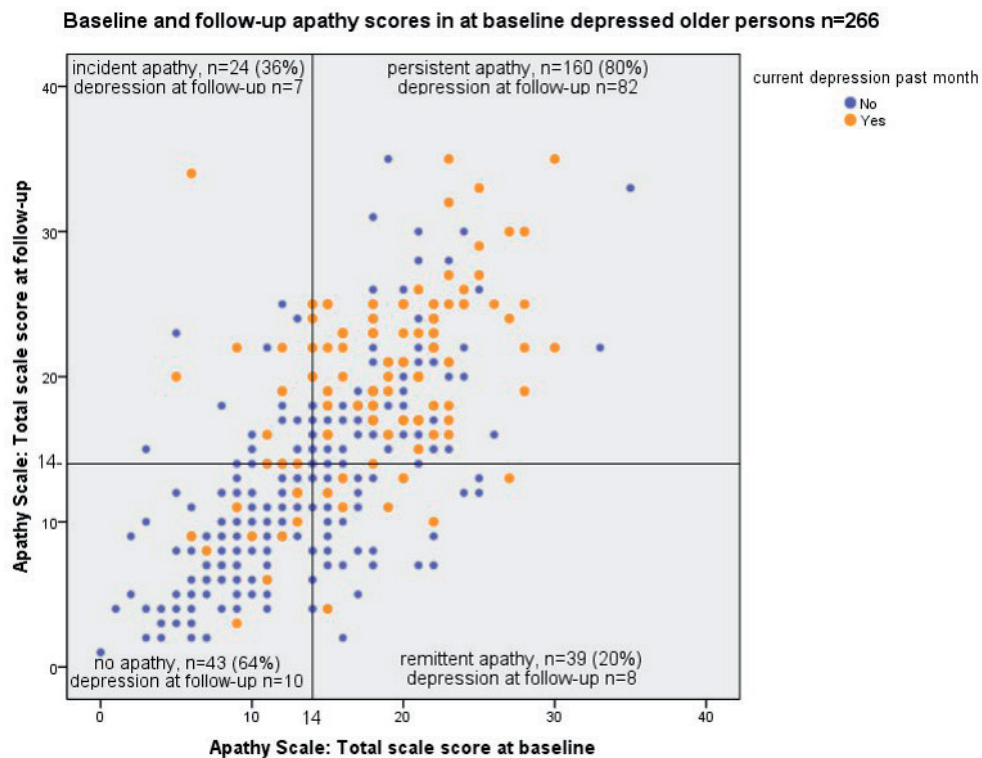


Figure 2. Incident (36%) and persistent apathy (80%), after 2 year follow-up, in older persons with a depressive disorder at baseline in and the relation with remission of the depressive disorder

Table 2 presents the sociodemographic and clinical characteristics of the older persons with depression without apathy at baseline and for those with and without apathy at follow-up. Univariate analyses showed that older persons with depression having incident apathy at 2-year follow-up had lower physical activity at baseline.

Table 2. Sociodemographic and clinical characteristics of older persons with depression without apathy at baseline for comparison of baseline characteristics between persons with and without apathy at follow-up (n=67)

	No Apathy at Baseline (n=67, 25%)				Univariate Analyses			
	No Apathy at Follow-up (n=43, 64%)		Apathy at Follow-up (n=24, 36%)		OR	W	95%CI	p-value
Sociodemographic characteristics								
Age in years, mean (SD)	69	(8)	71	(8)	1	1.3	0.97-1.1	0.3
Female gender, n (%)	33	(77)	19	(79)	1.2	0.5	0.3-3.9	0.8
Education in years, n (%)	10	(9-15)	11	(9-15)	1	0.03	0.9-1.2	0.9
Current partner, n (%)	21	(49)	13	(54)	1.2	1.8	0.5-3.4	0.7
Clinical characteristics								
Total chronic disease, mean (SD)	1.9	(1.3)	2	(1.4)	1.1	0.2	0.7-1.6	0.7
Cardiovascular disease, n (%) ^a	11	(26)	7	(29)	1.2	0.1	0.4-3.7	0.8
Diabetes mellitus, n (%)	5	(12)	2	(8)	0.7	0.1	0.1-4.1	0.7
Number of medications used, median (IQR)	5	(3-7)	4	(3.3-7)	0.99	0.004	0.8-1.2	0.95
Psychotropic medication, n (%) ^b	35	(81)	20	(83)	1.1	0.04	0.3-4.3	0.8
Analgesic medication, n (%) ^c	11	(26)	5	(21)	0.8	0.2	0.2-2.5	0.7
Benzodiazepine, n (%)	14	(33)	7	(29)	0.9	0.08	0.3-2.5	0.8
Antipsychotics, n (%)	4	(9)	4	(17)	2	0.8	0.4-8.6	0.4
Antidepressives, n (%)	26	(61)	18	(75)	2	1.4	0.6-6	0.2
Neuropsychiatric characteristics								
IDS score, median (IQR)	21	(15-31)	21	(12-30)	1	0.3	0.9-1	0.6
AS score, median (IQR)	10	(8-12)	12	(10-12)	1.2	2	0.9-1.4	0.2
MMSE score, median (IQR) ^d	29	(28-30)	28	(26-29)	0.8	2.8	0.6-1	0.09
Stroop test - Interference task, median (IQR)	1.2	(0.8-1.4)	1.2	(0.8-1.4)	1.2	0.2	0.6-2.5	0.7
Biological characteristics								
Cardiovascular risk, median (IQR) ^e	6	(3-10)	6	(3-8)	1	0.05	0.9-1.1	0.8
Walking speed (sec), median (IQR) ^f	6	(5.5-6.8)	6.2	(5.3-7.3)	1.1	0.03	0.3-4.4	0.9
Glucose, median (IQR) ^f	5.8	(5.5-6.2)	5.4	(4.8-6)	0.1	2	0.006-2.3	0.2
Body mass index, median (IQR)	24.5	(22.7-27)	25	(22.8-29.6)	1	0.1	0.9-1.1	0.7
IPAQ (MET minutes), median (IQR) ^f	3520	(2869-4318)	2164	(1282-3653)	0.5	3.8	0.3-1	0.05
Depression present at follow-up, n (%)	10	(23)	7	(29)	1.4	0.3	0.4-4.2	0.6

Notes: Abbreviations: AS, Apathy Scale, 14-item self-rating; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; IDS, Inventory of Depressive Symptomatology, 30-item self-rating; IPAQ, International Physical Activities Questionnaire in MET minutes; IQR, interquartile range; MET, metabolic equivalent; MMSE, Mini-Mental State Examination; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SD, standard deviation; Syst. BP, systolic blood pressure.

Data are presented as number (percentage), mean (standard deviation), or median (interquartile range), where appropriate. Univariate logistic regression analyses with df = 1 for all variables, OR with 95% confidence intervals, and Wald χ^2 statistics.

^a Including heart disease, vascular disease, and stroke;

^b Psychotropic medication includes the use of benzodiazepines, antidepressants, and antipsychotic drugs;

^c Analgesic includes the use of peripheral working analgesic medication, NSAIDs and analid;

^d Participants with MMSE < 19 were excluded;

^e Computed with: $CVD = 1/(1 + e^{-k})$ with $k = -8.65 + 0.057 \times \text{age} - 0.61 \times \text{gender} + 0.749 \times \text{antihypertensive medication} + 0.008 \times \text{syst. BP} + 0.458 \times \text{smoking} + 0.18 \times \text{cholesterol} - 0.234 \times \text{HDL cholesterol} + 0.857 \times \text{DM}$;

^f Geometric mean and 95% CI.

Multivariate analyses including all variables with a p value ≤ 0.1 showed that only a lower baseline MMSE score independently predicted incident apathy (Table 3).

Table 3. Independent predictors for incident apathy in older persons with depression (n=67)

	OR	Multivariate analyses		
		95% CI	Wald	p-value
Age in years	1.0	0.9-1.1	0.6	0.5
Female gender	1.5	0.3-6.6	0.3	0.6
MMSE score	0.7	0.4-0.97	4.5	0.03
IPAQ	0.5	0.2-1.0	3.5	0.06

Notes: Abbreviations: CI, confidence interval; IPAQ, International Physical Activities Questionnaire in MET minutes; MMSE, Mini-Mental State Examination; OR, odds ratio.
Multivariate logistic regression analyses with df = 1 for all variables, odds ratios (OR) with 95% confidence intervals (CI), and Wald χ^2 statistics.
Multivariate analyses using variables that showed a significance level of $P < 0.1$ on the univariate analyses.

Of the 199 older persons with depression having apathy at baseline, 160 (80%) also had apathy at 2-year follow-up. Of these 199 persons, 82 (41%) had apathy and were also depressed at follow-up (Figure 2). Older persons with persistent apathy were more likely to be depressed at follow-up compared to those who remitted from apathy (51% versus 21%; Table 4).

Table 4 presents the sociodemographic and clinical characteristics of the older persons with depression having apathy at baseline and for those with and without apathy at follow-up. Univariate analysis showed that older persons with depression having persistent apathy at follow-up used less benzodiazepines and scored higher on both the IDS and Apathy Scale at baseline.

Table 4. Sociodemographic and clinical characteristics of older persons with depression having apathy at baseline for comparison of baseline characteristics between persons with and without apathy at follow-up (n=199)

	Apathy at Baseline (n=199, 75%)				Univariate Analyses			
	No Apathy at Follow-up (n=39, 20%)		Apathy at Follow-up (n=160, 80%)		OR	W	95%CI	p-value
Sociodemographic characteristics								
Age in years, mean (SD)	71	(6)	71	(7)	1	0.002	0.95-1	1
Female gender, n (%)	21	(54)	102	(64)	1.5	1.3	0.7-3.1	0.3
Education in years, median (IQR)	9	(9-11)	10	(9-12)	1	0.2	0.9-1.1	0.6
Current partner, n (%)	20	(51)	86	(54)	1.1	0.08	0.5-2.2	0.8
Clinical characteristics								
Total chronic disease, mean (SD)	1.8	(1.2)	2.3	(1.6)	1.3	3.4	0.99-1.6	0.07
Cardiovascular disease, n (%) ^a	11	(28)	59	(37)	1.5	1	0.7-3.2	0.3
Diabetes mellitus, n (%)	3	(8)	24	(15)	2.1	1.4	0.6-7.4	0.2
Number of medications used, median (IQR)	6	(3-7)	5	(3.3-8)	1	0.5	0.9-1.2	0.5
Psychotropic medication, n (%) ^b	35	(90)	142	(89)	0.9	0.03	0.3-2.8	0.9
Analgesic medication, n (%) ^c	13	(33)	54	(34)	0.002	1	0.5-2.1	1
Benzodiazepine, n (%)	22	(56)	60	(38)	0.5	4.5	0.2-0.9	0.03
Antipsychotics, n (%)	5	(13)	18	(11)	0.9	0.08	0.3-2.5	0.8
Antidepressives, n (%)	29	(74)	121	(76)	1.1	0.03	0.5-2.4	0.9
Neuropsychiatric characteristics								
IDS score, median (IQR)	31	(18-38)	32	(24-41)	1	4.6	1-1	0.03
AS score, median (IQR)	17	(15-20)	20	(18-22)	1.2	9.3	1-1.3	0.002
MMSE score, median (IQR) ^d	28	(27-29)	28	(27-29)	1	0.02	0.8-1.2	0.9
Stroop test – Interference task, median (IQR)	1.2	(0.9-1.9)	1.2	(0.9-1.5)	0.9	0.4	0.6-1.3	0.6
Biological characteristics								
Cardiovascular risk, median (IQR) ^e	8	(5-11)	7	(5-12)	1	0.93	0.97-1.1	0.3
Walking speed (sec), median (IQR) ^f	6.4	(5.7-7.1)	7.1	(6.6-7.5)	2	2	0.8-5.3	0.2
Glucose, median (IQR) ^f	5.6	(5.4-5.9)	5.8	(5.6-5.9)	2.6	0.6	0.3-2.7	0.4
Body mass index, median (IQR)	26	(24-29)	26	(23-29)	1	0.05	0.9-1.1	0.8
IPAQ (MET minutes), median (IQR) ^f	1669	(998-2790)	1639	(1372-1959)	0.98	0.006	0.7-1.5	0.9
Depression present at Follow-up, n (%)	8	(21)	82	(51)	4.1	10.8	1.8-9.4	0.001

Notes: Abbreviations: AS, Apathy Scale, 14-item self-rating; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; IDS, Inventory of Depressive Symptomatology, 30-item self-rating; IPAQ, International Physical Activities Questionnaire in MET minutes; IQR, interquartile range; MET, metabolic equivalent; MMSE, Mini-Mental State Examination; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SD, standard deviation; Syst. BP, systolic blood pressure.

Data are presented as number (percentage), mean (standard deviation), or median (interquartile range), where appropriate. Univariate logistic regression analyses with df = 1 for all variables, OR with 95% confidence intervals, and Wald χ^2 statistics.

^a Including heart disease, vascular disease, and stroke;

^b Psychotropic medication includes the use of benzodiazepines, antidepressants, and antipsychotic drugs;

^c Analgesic includes the use of peripheral working analgesic medication, NSAID's and analid;

^d Participants with MMSE < 19 were excluded;

^e Computed with: $CVD = 1/(1 + e^{-k})$ with $k = -8.65 + 0.057 \times \text{age} - 0.61 \times \text{gender} + 0.749 \times \text{antihypertensive medication} + 0.008 \times \text{syst. BP} + 0.458 \times \text{smoking} + 0.18 \times \text{cholesterol} - 0.234 \times \text{HDL cholesterol} + 0.857 \times \text{DM}$;

^f Geometric mean and 95% CI.

Multivariate analyses showed that a higher baseline Apathy Scale score and less use of benzodiazepines independently predicted the persistence of apathy at follow-up (Table 5).

Table 5. Independent predictors for persistent apathy in older persons with depression (n=199)

	OR	Multivariate analyses		
		95%CI	Wald	p-value
Age in years	1.0	0.95-1.1	0001	0.97
Female gender	1.5	0.7-3.4	1.1	0.30
Total chronic disease	1.2	0.9-1.5	0.9	0.30
Frequency of benzodiazepine use	0.4	0.2-0.8	6.6	0.01
IDS score	1	0.98-1.1	0.9	0.40
AS score	1.2	1-1.3	7.1	0.008

Notes: Abbreviations: AS, Apathy Scale, 14-item self-rating; CI, confidence interval; IDS, Inventory of Depressive Symptomatology, 30-item self-rating; OR, odds ratio.

Multivariate logistic regression analyses with df=1 for all variables, OR with 95% CI, and Wald χ^2 statistics. Multivariate analyses using variables that showed a significance level of $p < 0.1$ on the univariate analyses

All analyses were repeated with different cut-off scores on the Apathy Scale (13, 15 and 18) and yielded similar results.

Discussion

In this study, severity of apathy at follow-up was predicted by severity of apathy at baseline and, as hypothesized, the 2-year incidence of apathy in older persons with depression (36%) was predicted by worse global cognitive functioning at baseline and not by severity of depression. In addition, the 2-year persistence of apathy in older persons with depression (80%) was predicted by more severe apathy and less use of benzodiazepines at baseline but not by severity of depression. Further, as also hypothesized, persistent apathy was associated with less recovery from depression. In this older population with depression, the 2-year incidence of apathy was higher than the 1-year incidence rates reported by others (i.e. 17.5-22.6%) investigating community-based populations and patients with Alzheimer disease.³⁹⁻⁴¹ Data on apathy incidence rates in older populations with depression are lacking. In the present study the persistence rate of apathy in older persons with depression was much higher than the 43% apathy persistence rate found in older persons having a major depression after 12 weeks of treatment with escitalopram.¹⁰ This difference may be explained by the latter population being physically more healthy, since persons having severe medical illnesses, substance abuse, and usage of medication associated

with depression (i.e. steroids, α -methyl dopa, clonidine, reserpine, tamoxifen, and cimetidine) were excluded.¹⁰ Other reported percentages (22.1-51.7%)³⁹⁻⁴² relate to studies in different populations (community based and Alzheimer disease) and to the use of more global scales to measure apathy, like the Neuropsychiatric Inventory. Also, we used the Apathy Scale as a self-administered measure, that was earlier shown to have good psychometric properties in patients with Parkinson Disease²⁵ but may have resulted in higher scores. Sensitive questions may be answered more truthfully when self-administered, since the presence of an interviewer might influence scores towards more socially desirable answers. On the other hand, explanation of the items by an interviewer can solve misunderstandings, leading to more specific answers. We earlier found that when administrating the 15-item version of the Geriatric Depression Scale at old age as a self-report measure, scores were higher than when administrated as an observer-rated measure.⁴³

Since dysthymia is a chronic depressive condition, which differs from major and minor depression, this could have influenced our results. However, in the present study most of the persons with dysthymia also had a major depression (68 of the 72) at baseline; moreover, omitting from the analysis the 4 persons having dysthymia yielded similar results.

In the present older population with depression, diminished cognition at baseline predicted the incidence of apathy at 2-year follow-up. The only longitudinal study among 76 healthy older persons that examined the predictive value of diminished cognition on apathy found no relation between baseline MMSE scores and scores on the Apathy Evaluation Scale at follow-up; however, subjective cognitive decline, several years prior to baseline assessment, predicted higher apathy scores at follow-up.⁴⁴ On the other hand, many studies on persons with Parkinson disease,^{45,46} mild cognitive impairment, or dementia^{6,39,40,47} and in community-based older persons⁴¹ found apathy, and not depression, to be a predictor of cognitive decline at follow-up. Therefore, apathy might be more a predictor or consequence of cognitive decline and dementia, rather than a symptom of depression.

Higher apathy scores are associated with more severe depressive symptoms, mainly related to negative symptoms.^{11,48} However, whether severe depressive symptoms can result in the emergence or continued existence of apathy over time is unknown. The present study shows that severity of depressive symptoms do not predict the onset or permanence of apathy at 2-year follow-up, which suggests a different etiology for apathy and depression. Alternatively, high Apathy Scale scores at baseline predict apathy at follow-up and poor recovery from depression. This is in line with case-control studies in older persons with depression having apathy, showing poor response to antidepressants⁸ and increased disability.¹⁰ This highlights the need to acknowledge that in older persons with depression, apathy may need a different treatment approach than that for depression.

In our study, surprisingly, less use of benzodiazepines at baseline was an independent predictor of the persistence of apathy at follow-up. In contrast, a cross-sectional study showed that more use of benzodiazepines in patients having apathy with Huntington disease predicted persistent apathy and suggested that apathy could be a side effect of this use.⁴⁹ Therefore, we performed additional analyses on benzodiazepine use in our sample; results showed a reduced use in older persons who recovered from apathy but a continued use of benzodiazepines in persons with persistent apathy at 2-year follow-up (data not shown). This might explain our counterintuitive finding that less use of benzodiazepines at baseline predicted persistent apathy.

Although the presence of cerebrovascular disease is a common cause of both depression and apathy, in our present study no association was found between cerebrovascular disease and incident or persistent apathy. Since we used a self-report measure to assess cerebrovascular diseases, this may have biased the results. Unfortunately, our study lacked imaging investigations (such as magnetic resonance imaging), which would have shown cerebrovascular damage more precisely.

A strength of this study is that it is the first longitudinal study to report the incidence and course of apathy in older persons with depression. Most studies on apathy are cross-sectional, and the longitudinal studies were mainly performed in community-based and clinical populations, for example, patients with mild cognitive impairment, Alzheimer disease, or poststroke symptoms.^{13,39-41,44,47,50} In addition, in our population, both depression and apathy were diagnosed using well-established validated measures. Some limitations are also present. First, of the 378 persons included at baseline, 24.6% was lost to follow-up due to death, or because of refusal/inability to participate further. Loss to follow-up was mainly among participants who had severe psychopathology at baseline, probably resulting in an underestimation of the presence of apathy at follow-up. Secondly, because at baseline 75% of the participants showed apathy, only a small sample was without apathy; this lack of power may be a reason for not being able to demonstrate (more) predictors for incident apathy. Thirdly, persistent apathy is difficult to establish because the Apathy Scale assesses apathy over the past 4 weeks only, and we have no data on the presence of apathy symptoms during the 2-year follow-up. Fourthly, since multiple comparisons were performed, it is possible that we found a statistically significant difference on an individual test (type 1 error) by chance. However, when this small chance (1 of 20) of finding a type 1 error is reduced by lowering the level of significance, the chance of finding no difference or effect, even though there is actually an effect (type 2 error), is increased.⁵¹ Furthermore, the Bonferroni correction, which is used to limit type 1 error, is found to be too conservative when testing for the significance of an association using equally correlated variables.⁵¹ Therefore, Bonferroni correction was not applied, since the chance on finding a type 1 error is very small, and our results are in accordance with other studies. Fifthly, we were unable to adjust for the effect of electroconvulsive treatment (ECT) since no

information was available on the use of ECT. However, only 25 older persons were hospitalized at baseline, which is a prerequisite for ECT in the Netherlands. Since not all hospitalized patients will have received ECT, this could only marginally have influenced our results. Finally, we dichotomized the scores on the Apathy Scale in accordance with the results from psychometric studies in Parkinson disease, using a cut-off score of 14.^{24,25} This could have led to underestimation or overestimation of the presence of apathy. However, performance of additional analyses using different cut-off scores of the Apathy Scale yielded similar results.

Conclusion

In our study population, both incidence and persistence rates of apathy at follow-up were high (36% and 80%, respectively), but neither was predicted by severity of depression. Poorer cognitive function predicted incident apathy, whereas more serious apathy at baseline predicted persistent apathy at follow-up, which was associated with less recovery from depression. Thus, clinically relevant apathy in older persons with depression that persists over time is associated with a worse prognosis for recovery from depression and should be seen as a behavioral syndrome in its own right. This persistence of apathy might be explained by the presence of residual symptoms of depression, which is in line with our findings, but can also be caused by psychotropic medication use or underlying cognitive impairment. Furthermore, when depression is accompanied by cognitive decline in older persons without apathy, this could result in developing clinically relevant apathy over time with poor prognosis as a result. These findings underpin the urgency to develop adequate diagnostic and treatment programs for older persons with depression also having clinically relevant apathy. Future studies should focus on early diagnosis and treatment of depression and apathy, keeping in mind a possible difference in their etiology.

References

1. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci.* 1998;10:314-319.
2. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry.* 2008;79:1088-1092.
3. Robert P, Onyike CU, Leentjens AF, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry.* 2009;24:98-104.
4. Onyike CU, Sheppard JM, Tschanz JT, et al. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry.* 2007;15:365-375.
5. Lenze EJ, Skidmore ER, Dew MA, et al. Does depression, apathy or cognitive impairment reduce the benefit of inpatient rehabilitation facilities for elderly hip fracture patients? *Gen Hosp Psychiatry.* 2007;29:141-146.
6. Lavretsky H, Zheng L, Weiner MW, et al. Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. *Am J Psychiatry.* 2010;167:589-597.
7. Groeneweg-Koolhoven I, de Waal MW, van der Weele GM, Gussekloo J, van der Mast RC. Quality of life in community-dwelling older persons with apathy. *Am J Geriatr Psychiatry.* 2014;22:186-194.
8. Levkovitz Y, Sheer A, Harel EV, et al. Differential effects of deep TMS of the prefrontal cortex on apathy and depression. *Brain Stimul.* 2011;4:266-274.
9. Lavretsky H, Lesser IM, Wohl M, Miller BL, Mehringer CM. Clinical and neuroradiologic features associated with chronicity in late-life depression. *Am J Geriatr Psychiatry.* 1999;7:309-316.
10. Yuen GS, Bhutani S, Lucas BJ, et al. Apathy in Late-Life Depression: Common, Persistent, and Disabling. *Am J Geriatr Psychiatry.* 2015;23:488-394.
11. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord.* 1993;28:117-124.
12. Leontjevas R, van Hooren S, Waterink W, Mulders A. Apathy and depressive mood in nursing home patients with early-onset dementia. *Am J Alzheimers Dis Other Demen.* 2009;24:341-348.
13. van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry.* 2008;23:266-271.
14. Maas DW, van der Mast RC, de Craen AJ. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry.* 2009;24:1177-1184.
15. Ligthart SA, Richard E, Fransen NL, et al. Association of Vascular Factors With Apathy in Community-Dwelling Elderly Individuals Vascular Factors and Apathy. *Arch Gen Psychiatry.* 2012;69:636-642.

16. Leontjevas R, Teerenstra S, Smalbrugge M, et al. More insight into the concept of apathy: a multidisciplinary depression management program has different effects on depressive symptoms and apathy in nursing homes. *Int Psychogeriatr*. 2013;25:1941-1952.
17. Yuen GS, Gunning FM, Woods E, Klimstra SA, Hoptman MJ, Alexopoulos GS. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *J Affect Disord*. 2014;166:179-186.
18. Wongpakaran N, van Reekum R, Wongpakaran T, Clarke D. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Ann Gen Psychiatry*. 2007;6:7.
19. Fava M. Pharmacological approaches to the treatment of residual symptoms. *J Psychopharmacol*. 2006;20:29-34.
20. Padala PR, Padala KP, Monga V, Ramirez DA, Sullivan DH. Reversal of SSRI-associated apathy syndrome by discontinuation of therapy. *Ann Pharmacother*. 2012;46:e8.
21. Comijs HC, van Marwijk HW, van der Mast RC, et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res Notes*. 2011;4:524.
22. Comijs HC, Nieuwesteeg J, Kok R, et al. The two-year course of late-life depression; results from the Netherlands study of depression in older persons. *BMC Psychiatry*. 2015;15:20.
23. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res*. 1991;38:143-162.
24. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4:134-139.
25. Pedersen KF, Alves G, Larsen JP, Tysnes OB, Moller SG, Bronnick K. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *Am J Geriatr Psychiatry*. 2012;20:142-148.
26. Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry*. 2001;158:872-877.
27. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. *Stroke*. 1993;24:1625-1630.
28. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26:477-486.
29. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
30. Korten NC, Penninx BW, Kok RM, et al. Heterogeneity of late-life depression: relationship with cognitive functioning. *Int Psychogeriatr*. 2014;26(6):953-963.
31. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643-662.
32. Penninx BW, Beekman AT, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res*. 2008;17:121-140.

33. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol*. 1996;49:1407-1417.
34. Norwegian Institute of public health. Anatomical Therapeutic Chemical Classification with used daydoses. WHO Collaborating Centre for Drug Statistics, 2011. http://www.whocc.no/atc_ddd_index/.
35. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci*. 2000;55:M221-M231.
36. Craig CL, Marshall AL, Sjoström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381-1395.
37. Weatherley ND, Jackson PR. The new Sheffield risk and benefit tables for the elderly. *QJM*. 2011;104:3-12.
38. Kant R, Duffy JD, Pivovarnik A. Prevalence of apathy following head injury. *Brain Inj*. 1998;12:87-92.
39. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2006;77:8-11.
40. Lechowski L, Benoit M, Chassagne P, et al. Persistent apathy in Alzheimer's disease as an independent factor of rapid functional decline: the REAL longitudinal cohort study. *Int J Geriatr Psychiatry*. 2009;24:341-346.
41. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr*. 2010;22:819-829.
42. Turro-Garriga O, Lopez-Pousa S, Vilalta-Franch J, et al. A longitudinal study of apathy in patients with Alzheimer's disease. *Rev Neurol*. 2009;48:7-13.
43. de Waal MW, van der Weele GM, van der Mast RC, Assendelft WJ, Gussekloo J. The influence of the administration method on scores of the 15-item Geriatric Depression Scale in old age. *Psychiatry Res*. 2012;197:280-284.
44. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int Psychogeriatr*. 2010;22:426-436.
45. Dujardin K, Sockeel P, Delliaux M, Destee A, Defebvre L. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Mov Disord*. 2009;24:2391-2397.
46. Oguru M, Tachibana H, Toda K, Okuda B, Oka N. Apathy and depression in Parkinson disease. *J Geriatr Psychiatry Neurol*. 2010;23:35-41.
47. Brodaty H, Burns K. Nonpharmacological management of apathy in dementia: a systematic review. *Am J Geriatr Psychiatry*. 2012;20:549-564.

48. Lampe IK, Heeren TJ. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *Int Psychogeriatr*. 2004;16:481-486.
49. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. *J Neuropsychiatry Clin Neurosci*. 2010;22:287-294.
50. Steinberg M, Shao H, Zandi P, Lyketsos CG, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry*. 2008;23:170-177.
51. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ*. 1998;316:1236-1238.



Chapter 5

Apathy in early- and late-life depression

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Abstract

Background

Late-life depression is thought to differ in clinical presentation from early-life depression. Particularly, late-life depression is considered to be more characterized by apathy than is early-life depression. Lacking convincing evidence, this study examines the presence and associated sociodemographic/clinical characteristics of apathy in older compared to younger depressed persons.

Methods

This cross-sectional study used data from two naturalistic cohort studies, i.e. the Netherlands Study of Depression in Older Persons (NESDO) and the Netherlands Study of Depression and Anxiety (NESDA). These studies included 605 persons (aged 18–93 years) with a major depressive disorder, divided into 217 early-life (< 60 years) and 388 late-life (≥ 60 years) depressed persons. Apathy was considered present if a score of ≥ 14 on the Apathy Scale.

Results

Apathy was strongly associated with age: it was more frequently present in persons with late-life depression (74.5%) than in those with early-life depression (53.5%). Independent of age, the following characteristics were associated with the presence of apathy: male gender, low education, use of benzodiazepines, chronic diseases, and more severe depression. Of all potential risk factors, only former and current smoking was associated with the presence of apathy in older depressed persons but not in younger depressed persons (p-value for age interaction = 0.01).

Limitations

No causal relationships can be drawn due to the cross-sectional design of the study.

Conclusions

In depressed individuals, clinically relevant apathy was more frequently present in older compared to younger persons. Both age groups showed largely the same associated risk factors. Apathy was independently associated with older age, male gender and more severe depression.

Introduction

Depression is one of the most prevalent psychiatric disorders, affecting 5-8% of the population worldwide.¹ It is often stated that depressive symptoms differ between younger and older depressed persons. For example, studies have demonstrated that late-life compared to early-life depressed persons show increased psychomotor retardation, decreased activity¹⁻³ and less mood symptoms (i.e. feelings of guilt),^{1,4-6} all of which resemble symptoms of apathy. Therefore, apathy may be considered to be a characteristic feature of especially late-life depression.¹ However, Apathy (as a clinically relevant syndrome) can be diagnosed when a cluster of clinical features is present (consisting of a loss of motivation, interest and concern) resulting in decreased goal-directed behavior, emotional responsivity and cognitive activity.

Distinguishing apathy (as a syndrome) from depression can be a major challenge due to an overlap in symptoms, e.g. loss of interest, which is also found in anhedonia. Although both apathy and anhedonia indicate lack/decrease of interest, the latter presents a state of decreased experienced pleasure in activities, whilst apathy is characterized by a lack of primary motivation and affective dullness.^{7,8}

Studies in different populations show that the following risk factors are associated with apathy as a clinically relevant syndrome in old age: vascular disease, excessive use of alcohol, use of benzodiazepines, smoking and the presence of chronic diseases.⁹⁻¹⁹ The few studies on clinically relevant apathy in depressed persons have focused mainly on older populations. In one cross-sectional study in depressed older persons: i) clinically relevant apathy was associated with severity of depression; whereas, longitudinally: ii) impaired cognitive function at baseline predicted incident apathy, and iii) more severe apathy at baseline predicted persistence of apathy and depression, whereas iv) remitted apathy was associated with less use of benzodiazepines.²⁰ In addition, no association was found between apathy and the use of antidepressants or presence of cardiovascular diseases.²⁰ Further, apathy appeared to be a predictor of poor response to antidepressant treatment,^{21,22} chronicity of depression,^{20,23} a poor prognosis, and increased overall mortality rates.^{24,25} Improved treatment of clinically relevant apathy within a depressed group would ameliorate the prognosis. Therefore, it is of clinical relevance to have better understanding of the position of clinically relevant apathy in depressed persons.¹⁻³

Systematic studies measuring the same apathy concept in late-life and early-life depression are lacking. Consequently, it is unknown whether apathy as a distinct and clinically relevant syndrome is indeed much less present in depressed younger persons than in depressed older persons; and, if so, whether apathy has similar associating sociodemographic and clinical correlates in older depressed persons compared to younger depressed persons.

Therefore, the present study examines whether: the prevalence of apathy (as a distinct clinically relevant syndrome) differs between late-life and early-life depression and whether certain late-life comorbidities (e.g. chronic diseases, atherosclerosis, severity of depression, use of alcohol, use of benzodiazepines and smoking) partly explain such an age difference. In addition, we examined whether the found determinants of apathy are more important (moderating) in late-life than in early-life.

Methods

Study design

This cross-sectional study is part of the Netherlands Study of Depression in Older persons (NESDO) and the Netherlands Study of Depression and Anxiety (NESDA). Both are multi-site naturalistic, prospective cohort studies designed to examine the psychosocial, neurobiological and clinical determinants, course and consequences of depressive disorders. All participants were recruited from general practices, mental healthcare organizations, and university medical centers. Exclusion criteria were: a diagnosis of dementia or a Mini Mental State Examination score (MMSE) ≤ 18 (only NESDO), the presence of another primary psychiatric disorder (e.g. psychotic or bipolar disorder), and insufficient mastery of the Dutch language.

The design of these studies are largely similar in scope and are described in earlier reports.^{26,27} Apathy was measured in both waves of NESDO as well as in the 6 year follow-up of NESDA. The main differences between the two studies are the inclusion of both depression and anxiety disorders in the NESDA study, whereas the NESDO study included persons suffering from depression alone, and also included inpatients (n=26). For the current analysis we used i) baseline data of the NESDO participants (age range 60-93 years) but excluding their inpatients, and ii) the 6-year follow-up data from the NESDA study (age range 24-71 years). From these studies, we included only the 605 participants who, irrespective of age of onset of depression, had a current (6-month recency) diagnosis of major depressive disorder (217 early-life, 388 late-life) according to the DSM-IV criteria (American Psychiatric Association) as assessed with the Composite International Diagnostic Interview; CIDI; WHO version 2.1; life-time version)²⁸ and who had completed Apathy Scale scores. Early-life (< 60 years) and late-life (≥ 60 years) depression was defined using a cut-off age of 60 years, which is mostly commonly used.^{2,29,30}

Both study protocols were approved by the Ethical Review Boards of all the participating centers. Before enrollment all participants gave written informed consent.

Measures

Assessment of apathy

Apathy was assessed with the Apathy Scale, used as a self-report questionnaire that has demonstrated good psychometric properties.^{31,32} The Apathy Scale consists of 14 items with four possible answers ranging from 0 to 3 (maximum 42) points^{31,32}; higher scores indicate more severe apathy.³¹ In different clinical populations, a cut-off score of 14 showed a moderate sensitivity and a high specificity for the presence of clinically relevant apathy.³¹⁻³⁴

Assessment of presence and severity of depression

The presence of a depressive disorder in the 6 months before the measurement was assessed with the CIDI (WHO version 2.1; life-time version).²⁸

The severity of depressive symptoms was assessed using the 30-item self-report Inventory of Depressive Symptomatology (IDS-SR)³⁵ with higher scores indicating more severe depression.

Assessment of other characteristics

For all participants, information was obtained on gender, age, and education. Education was divided into three levels: basic (0-8 years), intermediate (9-14 years), and high (>15 years).³⁶

For the assessment of chronic diseases, a self-rating questionnaire was used asking the participants whether they currently or previously had any of the following chronic diseases or disease events: cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, lung disease, osteoarthritis or cancer, or any other disease.^{26,27} The accuracy of self-report of these diseases has shown to be adequate and independent of cognitive impairment compared to data obtained from general practitioners.³⁷ The self-reported use of benzodiazepines (on a only daily basis only), i.e. anxiolytics and hypnotics, was classified using the Anatomical Therapeutic Chemical Classification system.³⁸ The number of alcoholic drinks a day was assessed with the Alcohol use Disorders Identification Test (AUDIT).³⁹

Smoking status was defined as non-smoker, former smoker or current smoker. The ankle/brachial index (ABI) was used as an indicator of peripheral atherosclerosis. Doppler assessment (with an electronic Omron sphygmomanometer) of ankle and arm systolic blood pressure enabled to calculate the ABI.⁴⁰

Statistical analysis

Data are presented as numbers with percentages, medians with interquartile ranges (IQR), or means with standard deviations (SD), where appropriate. Using univariate analyses, persons with late-life (≥ 60 years) depression and early-life (< 60 years) depression were compared with regard to the presence and severity of apathy, severity

of depression, chronic diseases, atherosclerosis, use of alcohol, use of benzodiazepines, and smoking.

To further examine correlates of clinically relevant apathy in late-life and early-life depression, logistic and multivariable regression analyses were performed in the total group of depressed persons adjusted for severity of depression. Additionally, to investigate whether the association between apathy and late-life depression is moderated by specific late-life comorbidities, both an interaction term age*potential risk factor and an ELD/LLD*potential risk factor were studied in the regression model that was adjusted for severity of depression. We present the results of age as a continuous instead of a dichotomous (early-life versus late-life) measure, since this yields more sensitivity. The continuous variable age was centered to avoid multicollinearity. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed. A p-value < 0.05 was considered statistically significant.

For sensitivity analysis, all analyses were repeated using age as a continuous variable in the interaction term and using cut-off scores of 13, 15 and 18 on the Apathy Scale.⁴¹ Statistical analyses were performed with SPSS 22.0 (IBM for Windows).

Results

Table 1 presents the characteristics of early-life and late-life depressed persons. The two groups with early-life depression (mean age 43.6, SD 9.8 years) and late-life depression (mean age 69.7, SD 7.3 years) showed no significant difference in gender (71.4% and 66% female gender, respectively).

Compared to early-life depression, persons with late-life depression had a lower educational level, more chronic diseases, more often used benzodiazepines, were more often former smokers, used more alcohol, and had a lower mean ABI. Furthermore, in late-life depressed persons, clinically relevant apathy according to an Apathy Scale score ≥ 14 was significantly more often present (also when corrected for severity of depression) and their mean Apathy Scale score and IDS score were higher, compared to early-life depressed persons, regardless of age of onset of depression in persons with late-life depression.

Table 1. Sociodemographic and clinical characteristics of early-life depression and late-life depression.

	Type of depression				p-value
	Early-life (18-60 years) n=217		Late-life (≥60 years) n=363		
Demographic characteristics					
Age in years, mean (SD)	43.6	(9.8)	69.7	(7.3)	<0.001**
Female gender, n (%)	155	(71.4)	240	(66)	0.2*
Education, n (%)					<0.001*
Basic	12	(5.5)	75	(20.7)	
Intermediate	112	(51.6)	202	(55.6)	
High	93	(42.9)	86	(23.7)	
Clinical characteristics					
Chronic diseases, median (IQR)	1.0	(0 – 1)	2.0	(1 – 3)	<0.001***
Generalized atherosclerosis ^a , mean (SD)	1.2	(0.1)	1.1	(0.2)	<0.001**
Use of alcohol ^b , median (IQR)	0.03	(0-0.1)	0.03	(0-1.2)	0.001***
Use of benzodiazepines, n (%)	14	(6.5)	123	(33.9)	<0.001*
Smoking, n (%)					<0.001*
Never	85	(39.2)	95	(26.2)	
Former	55	(25.3)	162	(44.6)	
Current	76	(35.0)	107	(28.4)	
Neuropsychiatric characteristics					
Depression score ^c , mean (SD)	27.3	(11.1)	30.0	(13)	0.01**
Apathy					
Present, n (%)	116	(53.5)	269	(74.1)	<0.001*
Total score, mean (SD)	14.3	(5.0)	17.0	(5.5)	<0.001**

Note: Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.

Comparison using *Chi square, **T tests or ***Mann-Whitney test.

^aMeasured by the ankle-brachial index

^bAUDIT: Daily alcohol consumption

^cMeasured by the Inventory of Depressive Symptomatology, 30 self-rating items

In the whole group of depressed persons, higher severity of depression was associated with the presence of apathy. When, corrected for severity of depression, the following were also associated with the presence of apathy: male gender, lower education, more chronic diseases, more use of benzodiazepines (Table 2).

Table 2. Logistic regression analyses of the total group of depressed persons (n=580) with and without apathy and the effect of the interaction term age, all corrected for depression severity.

	Apathy absent n=195	Apathy present n=385	OR (95% CI) Adjusted ^d	Wald	p-value	Interaction term age_centered p-value
Demographic characteristics						
Age in years, mean (SD)	55 (16)	62 (14)	1.03 (1.02-1.05)	26.78	<0.001	
Female gender, n (%)	148 (76)	247 (64)	0.52 (0.35-.78)	9.99	0.002	0.6
Education, n (%)		0				
Basic	20 (10)	67 (17)	reference			
Intermediate	100 (51)	214 (56)	0.79 (0.45-1.42)	0.60	0.4	0.4
High	75 (39)	104 (27)	0.52 (0.28-0.95)	4.58	0.03	0.8
Clinical characteristics						
Chronic diseases, median (IQR)	1 (0-2)	1 (1-3)	1.22 (1.06-1.41)	7.71	0.005	0.98
Generalized atherosclerosis ^a , mean (SD)	1.1 (0.15)	1.1 (0.19)	0.75 (0.25-2.22)	0.27	0.6	0.02
Use of alcohol ^b , median (IQR)	0.03 (0-0.4)	0.04 (0-0.5)	1.24 (0.94-1.62)	2.33	0.1	0.6
Use of benzodiazepines, n (%)	32 (16)	105 (27)	1.63 (1.03-2.57)	4.37	0.04	0.7
Smoking, n (%)						
Never	68 (35)	112 (29)	reference			
Former	65 (33)	152 (40)	1.47 (0.96-2.28)	3.07	0.08	0.04
Current	60 (31)	119 (31)	1.9 (0.76-1.87)	0.60	0.4	0.04
Neuropsychiatric characteristics						
Depression score ^c , mean (SD)	24 (12)	31 (12)	1.05 (1.03-1.07)	35.99	<0.001	0.8
Late life depression, n (%)	94 (48)	269 (70)	2.40 (1.66-3.46)	21.74	<0.001	
Apathy						
Total score, mean (SD)	10 (3)	19 (4)				

Note: Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.

^aMeasured by the ankle-brachial index

^bAUDIT: Daily alcohol consumption;

^cMeasured by the Inventory of Depressive Symptomatology, 30 self-rating items, unadjusted

^dOR adjusted for depression severity

Of all eight individual interaction terms, only 'age x smoking' and 'age x ABI' were associated with the presence of apathy. After stratification for early-life and late-life depression, older depressed persons with apathy were more often former and current smokers compared to older depressed persons without apathy (OR=1.74, 95% CI=0.99-3.03, $p=0.05$ and OR=2.05, 95% CI=1.08-3.89, $p=0.03$, respectively) (supplementary table, not shown). Younger depressed persons with apathy did not differ in their smoking habits from those without apathy (OR=0.73, 95% CI=0.37-1.44, $p=0.4$ and OR=0.66, 95% CI=0.36-1.24, $p=0.7$, respectively). However, both older and younger depressed persons with apathy had no difference in ABI compared with those without apathy (supplementary table, not shown).

Table 3 shows that, among the whole group of depressed persons, age (OR=1.0, 95% CI=1.01-1.04, $p<0.001$), male gender (OR=0.5, 95% CI=0.35-0.80, $p=0.003$) and higher IDS (OR=1.1, 95% CI=1.04-1.06, $p<0.001$) scores were independent correlates of apathy. All analyses were repeated with different cut-off scores on the Apathy Scale (i.e. 13, 15, and 18), which yielded similar results.

Table 3. Independent correlates of apathy in depressed persons (n=580)

	Multivariable analyses			
	OR	95%CI	Wald	P
Age in years	1.0	1.01-1.04	12.6	<0.001
Female gender	0.5	0.35-0.80	9.0	0.003
Education	0.9	0.63-1.17	0.9	0.3
Chronic diseases	1.1	0.9-1.24	0.4	0.5
Use of benzodiazepines	1.2	0.7-1.9	0.4	0.6
Depression score	1.1	1.04-1.06	26.8	<0.001

Note: Multivariable analyses using variables (table 2) that showed a significance level of $p<0.05$ on analyses
Depression score: Inventory of Depressive Symptomatology, 30-items self-rating

Discussion

In this study, apathy as a clinically relevant syndrome, was more often present in older depressed persons (269/363; 75%) compared to younger depressed persons (116/217; 54%) and was also more severe in the older group, independent of the severity of depression.

In the whole group of depressed persons, apathy was associated with male gender, lower education, more frequent use of benzodiazepines, more chronic diseases and more severe depression. In older depressed persons, smoking was associated with the presence of clinically relevant apathy, which was not the case in younger depressed persons. In the whole group of depressed persons, apathy was independently associated with older age, male gender and more severe depression.

The presence of clinically relevant apathy in depressed older persons is in accordance with other studies.^{21,42-44} It is known that apathy, as assessed with the items 'psychomotor retardation' and 'decreased activity' of the Hamilton Rating Scale for Depression is often present in younger persons suffering from depression, although less often than in older depressed persons.¹⁻³ The prevalence and associating factors of apathy as a clinically relevant syndrome, operationalized as a cluster of clinical features according to the Apathy Scale, have not yet been examined before in younger depressed persons. The present study shows that, in more than half of the younger depressed persons, clinically relevant apathy was present; although, significantly less than in the older depressed group.

In late-life depression, the presence and severity of apathy is known for its negative influence on the prognosis and treatment response of depression.^{22,45-47} However, it is unknown whether clinically relevant apathy in younger depressed persons has a similar negative influence on the course of depression.

Apart from smoking, no differences in associating factors for apathy were found in early-life and late-life depression. Male gender, lower education, use of benzodiazepines, presence of chronic diseases, and a higher severity of depression are all reported to be associated with apathy in older depressed persons.^{18,48,49} However, in the present study, only (former and current) smoking was specifically related to the presence of apathy in late-life depression but not in early-life depression. This finding is partly in contrast with an earlier study reporting that current smokers, compared to long-term ex-smokers and never smokers (aged 19-58 years), scored significantly higher on the three-item subscale for apathy of the Frontal System Behavior Scale.¹² However, this subscale only scores some apathetic-type symptoms, rather than clinically relevant apathy as a syndrome according to the Apathy Scale. Cross-sectional studies in community-based older persons and stroke patients showed no association between current smoking and the presence of apathy in older persons.^{25,50} However, no studies have examined the long-term effects of smoking (duration of smoking in years and total cigarettes a day) on motivation.

In the present study, the ABI (as a measure for generalized atherosclerosis) was not associated with the presence of apathy in the separate age groups. This is in contrast to studies among community-based populations reporting that the presence of cerebrovascular disease and risk factors are associated with the presence of apathy.^{9,51} However, other studies among depressed older persons failed to show this association, probably due to different populations and the use of a more validated measurement to assess apathy.^{20,49} Also, age, male gender and severity of depression were independent correlates of apathy in the depressed group; this is in accordance with earlier reports.^{9,16,17,19,52}

The present study is the first to compare the presence, severity and correlates of apathy in early versus late-life depressed persons in a large sample. Earlier we examined the

presence, correlates and predictors of apathy in depressed older persons from the NESDO study. For this study we had the opportunity to enlarge the study population with data from the NEDA study, to examine differences between younger and older depressed persons concerning the presence and correlates of apathy. An important strength of the present study is that both depression and apathy were assessed using established validated measures.

Some limitations also need to be addressed. First, we cannot conclude whether depression, in the course of the time, is more associated with the presence of apathy, since this study has a cross-sectional design. Second, patients were recruited from primary care and from outpatient secondary care clinics, whereas inpatients from the NESDO cohort were excluded; this limits the generalizability of the results to more severe depressed inpatients. Third, the Apathy Scale was a self-report measure, which could have resulted in subjective underscore related the presence of apathy. Further, scores on the Apathy Scale were dichotomized in accordance with the results from psychometric studies in Parkinson and Alzheimer's disease using a cut-off score of 14,^{31,32} which may have led to under- or overestimation of the presence of clinically relevant apathy. However, additional post-hoc analyses using different cut-off scores of the Apathy Scale yielded similar results regarding the presence and correlates of apathy in older compared to younger depressed persons. Fourth, we had only partial information on cognitive functioning since the MMSE was conducted only in the NESDO cohort. In addition, in NESDO, we excluded individuals with (according to their clinician) a suspected diagnosis of dementia. Nevertheless, we may have included older persons with early dementia, because it is difficult to diagnose dementia when an individual is depressed. Therefore, we performed sensitivity analyses using a cut-off score of < 24 on the MMSE thereby excluding a total of 16 older persons; however these analyses yielded similar results. Fifth, we didn't compare the results with a non-depressed control group which limits generalisability of the results. Last, although the same measures were used to assess depression according to DSM-IV criteria and apathy in both cohorts, and inpatients from the NESDO study were excluded, differences between the two cohort studies might explain the higher presence of apathy found in the late-life depressed individuals. Also, since the recruitment of depressed persons from the NESDA study, but not the NESDO study, was also from the general population, this might have resulted in the inclusion of less severe depressed persons in the early-life depression group. In addition, global cognitive functioning was not assessed in the NESDA study, resulting in the inclusion of persons with a cognitive decline in the late-life depressed group.

In clinical setting, differentiating apathy from depression can be troublesome due to overlapping symptoms, such as diminished interest, activity and energy. However, apathy lacks mood-related symptoms and is primarily a motivational disorder showing a decrease in goal-directed behaviour, emotional blunting, indifference and loss of initiative⁵³⁻⁵⁵. Recognizing apathy as a clinical relevant syndrome accompanying

a depressive disorder is essential, since apathy predicts poor response of depressive symptoms to treatment, chronicity of depression and functional impairment.^{20,22,56}

In conclusion, our findings show that the presence and severity of clinically relevant apathy was significantly less in early-life depressed persons compared to late-life depressed persons showing that both older and younger depressed persons had largely the same associating risk factors, with the exception of smoking which was associated with the presence of apathy in older depressed persons only. Furthermore, in the entire study population age, male gender and severity of depression were independently associated with the presence of apathy.

Whether apathy as a clinical relevant syndrome in early-life depression has the same negative outcomes as in late-life depression remains unknown. Longitudinal studies are necessary to clarify the position and implications of apathy in early-life depressed persons on the long term.

References

1. Shahpesandy H. Different manifestation of depressive disorder in the elderly. *Neuro Endocrinol Lett.* 2005;26:691-695.
2. Brodaty H, Peters K, Boyce P, et al. Age and depression. *J Affect Disord.* 1991;23(3):137-149.
3. Brodaty H, Luscombe G, Parker G, et al. Increased rate of psychosis and psychomotor change in depression with age. *Psychol Med.* 1997;27:1205-1213.
4. Hegeman JM, Kok RM, van der Mast RC, Giltay EJ. Phenomenology of depression in older compared with younger adults: meta-analysis. *Br J Psychiatry.* 2012;200:275-281.
5. Lyness JM, Cox C, Curry J, Conwell Y, King DA, Caine ED. Older age and the underreporting of depressive symptoms. *J Am Geriatr Soc.* 1995;43:216-221.
6. Yates WR, Mitchell J, Rush AJ, et al. Clinical features of depressed outpatients with and without co-occurring general medical conditions in STAR*D. *Gen Hosp Psychiatry.* 2004;26:421-429.
7. Kaji Y, Hirata K. Apathy and anhedonia in Parkinson's disease. *ISRN Neurol.* 2011:219427.
8. Kirsch-Darrow L, Marsiske M, Okun MS, Bauer R, Bowers D. Apathy and depression: separate factors in Parkinson's disease. *J Int Neuropsychol Soc.* 2011;17:1058-1066.
9. van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry.* 2008;23:266-271.
10. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2010;22:287-294.
11. Lyvers M, Carlopio C, Bothma V, Edwards MS. Mood, mood regulation expectancies and frontal systems functioning in current smokers versus never-smokers in China and Australia. *Addict Behav.* 2013;38:2741-2750.
12. Lyvers M, Carlopio C, Vicole Bothma H, Edwards MS. Mood, mood regulation, and frontal systems functioning in current smokers, long-term abstinent ex-smokers, and never-smokers. *J Psychoactive Drugs.* 2014;46:133-139.
13. Winhusen TM, Somoza EC, Lewis DF, Kropp FB, Horigian VE, Adinoff B. Frontal systems deficits in stimulant-dependent patients: evidence of pre-illness dysfunction and relationship to treatment response. *Drug Alcohol Depend.* 2013;127:94-100.
14. Semprini R, Lubrano A, Misaggi G, Martorana A. Apathy as marker of frail status. *J Aging Res.* 2012; Doi: 10.1155/2012/436251.
15. Moselhy HF, Georgiou G, Kahn A. Frontal lobe changes in alcoholism: a review of the literature. *Alcohol Alcohol.* 2001;36:357-368.
16. Onyike CU, Sheppard JM, Tschanz JT, et al. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry.* 2007;15:365-375.
17. Adams KB. Depressive symptoms, depletion, or developmental change? Withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *Gerontologist.* 2001;41:768-777.

18. Maas DW, van der Mast RC, de Craen AJ. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry*. 2009;24:1177-1184.
19. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr*. 2010;22:819-829.
20. Groeneweg-Koolhoven I, Comijs HC, Naarding P, de Waal MW, van der Mast RC. Apathy in Older Persons With Depression: Course and Predictors: The NESDO Study. *J Geriatr Psychiatry Neurol*. 2016;29:178-186.
21. Wongpakaran N, van Reekum R, Wongpakaran T, Clarke D. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Ann Gen Psychiatry*. 2007;6:7.
22. Levkovitz Y, Sheer A, Harel EV, et al. Differential effects of deep TMS of the prefrontal cortex on apathy and depression. *Brain Stimul*. 2011;4:266-274.
23. Lavretsky H, Lesser IM, Wohl M, Miller BL, Mehringer CM. Clinical and neuroradiologic features associated with chronicity in late-life depression. *Am J Geriatr Psychiatry*. 1999;7:309-316.
24. Lavretsky H, Zheng L, Weiner MW, et al. Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. *Am J Psychiatry*. 2010;167:589-597.
25. Yasuda N, Mino Y, Koda S, Ohara H. The differential influence of distinct clusters of psychiatric symptoms, as assessed by the general health questionnaire, on cause of death in older persons living in a rural community of Japan. *J Am Geriatr Soc*. 2002;50:313-320.
26. Comijs HC, van Marwijk HW, van der Mast RC, et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res Notes*. 2011;4:524.
27. Penninx BW, Beekman AT, Smit JH, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res*. 2008;17:121-140.
28. Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *Br J Psychiatry*. 1991;159:645-653, 658.
29. Brodaty H, Cullen B, Thompson C, et al. Age and gender in the phenomenology of depression. *Am J Geriatr Psychiatry*. 2005;13:589-596.
30. Gournellis R, Oulis P, Rizos E, Chourdaki E, Gouzaris A, Lykouras L. Clinical correlates of age of onset in psychotic depression. *Arch Gerontol Geriatr*. 2011;52:94-98.
31. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4:134-139.

32. Pedersen KF, Alves G, Larsen JP, Tysnes OB, Moller SG, Bronnick K. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *Am J Geriatr Psychiatry*. 2012;20:142-148.
33. Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry*. 2001;158(6):872-877.
34. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. *Stroke*. 1993;24:1625-1630.
35. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26:477-486.
36. Prins MA, Verhaak PF, Smolders M, et al. Patient factors associated with guideline-concordant treatment of anxiety and depression in primary care. *J Gen Intern Med*. 2010;25:648-655.
37. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol*. 1996;49:1407-1417.
38. Norwegian, Institute of Public Health. Anatomical Therapeutic Chemical Classification with used daydoses.: WHO Collaborating Centre for Drugs Statistics; 2011.
39. Babor TF, Kranzler HR, Lauerma RJ. Early detection of harmful alcohol consumption: comparison of clinical, laboratory, and self-report screening procedures. *Addict Behav*. 1989;14:139-157.
40. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation*. 1993;88:837-845.
41. Kant R, Duffy JD, Pivovarnik A. Prevalence of apathy following head injury. *Brain Inj*. 1998;12:87-92.
42. Lampe IK, Heeren TJ. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *Int Psychogeriatr*. 2004;16:481-486.
43. Groeneweg-Koolhoven I, de Waal MW, van der Weele GM, Gussekloo J, van der Mast RC. Quality of life in community-dwelling older persons with apathy. *Am J Geriatr Psychiatry*. 2014;22:186-194.
44. Marin RS, Firinciogullari S, Biedrzycki RC. Group differences in the relationship between apathy and depression. *J Nerv Ment Dis*. 1994;182:235-239.
45. Vinkers DJ, Stek ML, Gussekloo J, Van Der Mast RC, Westendorp RG. Does depression in old age increase only cardiovascular mortality? The Leiden 85-plus Study. *Int J Geriatr Psychiatry*. 2004;19:852-857.
46. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am J Psychiatry*. 2005;162:1588-1601.

47. Uher R, Perlis RH, Henigsberg N, et al. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. *Psychol Med*. 2012;42:967-980.
48. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int Psychogeriatr*. 2010;22:426-436.
49. Groeneweg-Koolhoven IC, Hannie C; Naarding, Paul; de Waal, Margot MW; van der Mast, Roos Presence and correlates of apathy in non-demented depressed and non-depressed older persons. . *Eur. J. Psychiat*. 2015;29:119-130.
50. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - the Sydney Stroke Study. *Psychol Med*. 2005;35:1707-1716.
51. Ligthart SA, Richard E, Fransen NL, et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69:636-642.
52. Mehta M, Whyte E, Lenze E, et al. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *Int J Geriatr Psychiatry*. 2008;23:238-243.
53. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord*. Jun 1993;28:117-124.
54. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci*. 1998;10:314-319.
55. Leontjevas R, Teerenstra S, Smalbrugge M, et al. More insight into the concept of apathy: a multidisciplinary depression management program has different effects on depressive symptoms and apathy in nursing homes. *Int Psychogeriatr*. 2013;25:1941-1952.
56. Yuen GS, Bhutani S, Lucas BJ, et al. Apathy in Late-Life Depression: Common, Persistent, and Disabling. *Am J Geriatr Psychiatry*. 2015;23:488-494.

Table S1. Logistic regression analyses of the total group of depressed persons (n=580) with and without apathy, and the effect of the interaction term early-life depression (ELD) / late-life depression (LLD) and the interaction term age all corrected for depression severity.

	Apathy absent n=195	Apathy present n=385	OR (95% CI)	Wald	p-value	Interaction term ELD/LLD p-value	Interaction term age_centered p-value
Demographic characteristics							
Age in years, mean (SD)	55 (16)	62 (14)	1.03 (1.02-1.05)	26.78	<0.001		
Female gender, n (%)	148 (76)	247 (64)	0.52 (0.35-0.78)	9.99	0.002	0.3	0.6
Education, n (%)							
Basic	20 (10)	67 (17)	reference				
Intermediate	100 (51)	214 (56)	0.79 (0.45-1.42)	0.6	0.4	0.2	0.4
High	75 (39)	104 (27)	0.52 (0.28-0.95)	4.58	0.03	0.8	0.8
Clinical characteristics							
Chronic diseases, median (IQR)	1 (0-2)	1 (1-3)	1.22 (1.06-1.41)	7.71	0.005	0.9	0.98
Generalized atherosclerosis ¹ , mean (SD)	1.1 (0.15)	1.1 (0.19)	0.75 (0.25-2.22)	0.27	0.6	0.2	0.02
Use of alcohol ³ , median (IQR)	0.03 (0-0.4)	0.04 (0-0.5)	1.24 (0.94-1.62)	2.33	0.1	0.8	0.6
Use of benzodiazepines, n (%)	32 (16)	105 (27)	1.63 (1.03-2.57)	4.37	0.04	0.2	0.7
Smoking, n (%)							
Never	68 (35)	112 (29)	reference				
Former	65 (33)	152 (40)	1.47 (0.96-2.28)	3.07	0.08	0.03	0.04
Current	60 (31)	119 (31)	1.9 (0.76-1.87)	0.6	0.4	0.01	0.04
Neuropsychiatric characteristics							
Depression score ² , mean (SD)	24 (12)	31 (12)	1.05 (1.03-1.07)	35.99	<0.001	0.4	0.8
Late life depression, n (%)	94 (48)	269 (70)	2.40 (1.66-3.46)	21.74	<0.001		
Apathy							
Total score, mean (SD)	10 (3)	19 (4)					
Note: Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.							
¹ Measured by the ankle-brachial index							
² Measured by the Inventory of Depressive Symptomatology, 30 self-rating items							
³ AUDIT: Daily alcohol consumption							

Table S2. Logistic regression analyses of the total group (MMSE $\geq$ 25) of depressed persons (n=563) with and without apathy, and the effect of the interaction term age corrected for depression severity.

	Apathy absent n=190	Apathy present n=373	OR (95% CI)	Wald	p-value	Interaction term age_centered p-value
Demographic characteristics						
Age in years, mean (SD)	54 (16)	62 (14)	1.03 (1.02-1.05)	28.84	<0.001	
Female gender, n (%)	145 (76)	240 (64)	0.51 (0.34-.77)	10.28	0.001	0.5
Education, n (%)						
Basic	18 (10)	67 (17)	<i>reference</i>			
Intermediate	99 (52)	207 (56)	0.71 (0.39-1.29)	1.24	0.3	0.7
High	73 (38)	101 (27)	0.47 (0.25-0.88)	5.52	0.02	0.9
Clinical characteristics						
Chronic diseases, median (IQR)	1 (0-2)	1 (1-3)	1.25 (1.08-1.45)	9.21	0.002	0.6
Generalized atherosclerosis ¹ , median (IQR)	1.1 (0.15)	1.1 (0.19)	0.76 (0.25-2.27)	0.25	0.6	0.04
Use of alcohol ¹ , median (IQR)	0.03 (0-0.5)	0.06 (0-0.5)	1.21 (0.92-1.59)	1.86	0.2	0.7
Use of benzodiazepines, n (%)	29 (15)	99 (27)	1.73 (1.03-2.38)	5.20	0.02	0.4
Smoking, n (%)						
Never	66 (35)	108 (29)	<i>reference</i>			
Former	63 (33)	147 (39)	1.48 (0.95-2.30)	3.02	0.08	0.05
Current	60 (31)	116 (31)	1.17 (0.74-1.83)	0.44	0.5	0.06
Neuropsychiatric characteristics						
Depression score ² , mean (SD)	24 (12)	31 (12)	1.05 (1.03-1.07)	32.44	<0.001	0.8
Late life depression, n (%)	89 (45)	257 (69)	2.5 (1.70-3.57)	22.58	<0.001	
Apathy						
Total score, mean (SD)	10 (3)	19 (4)				

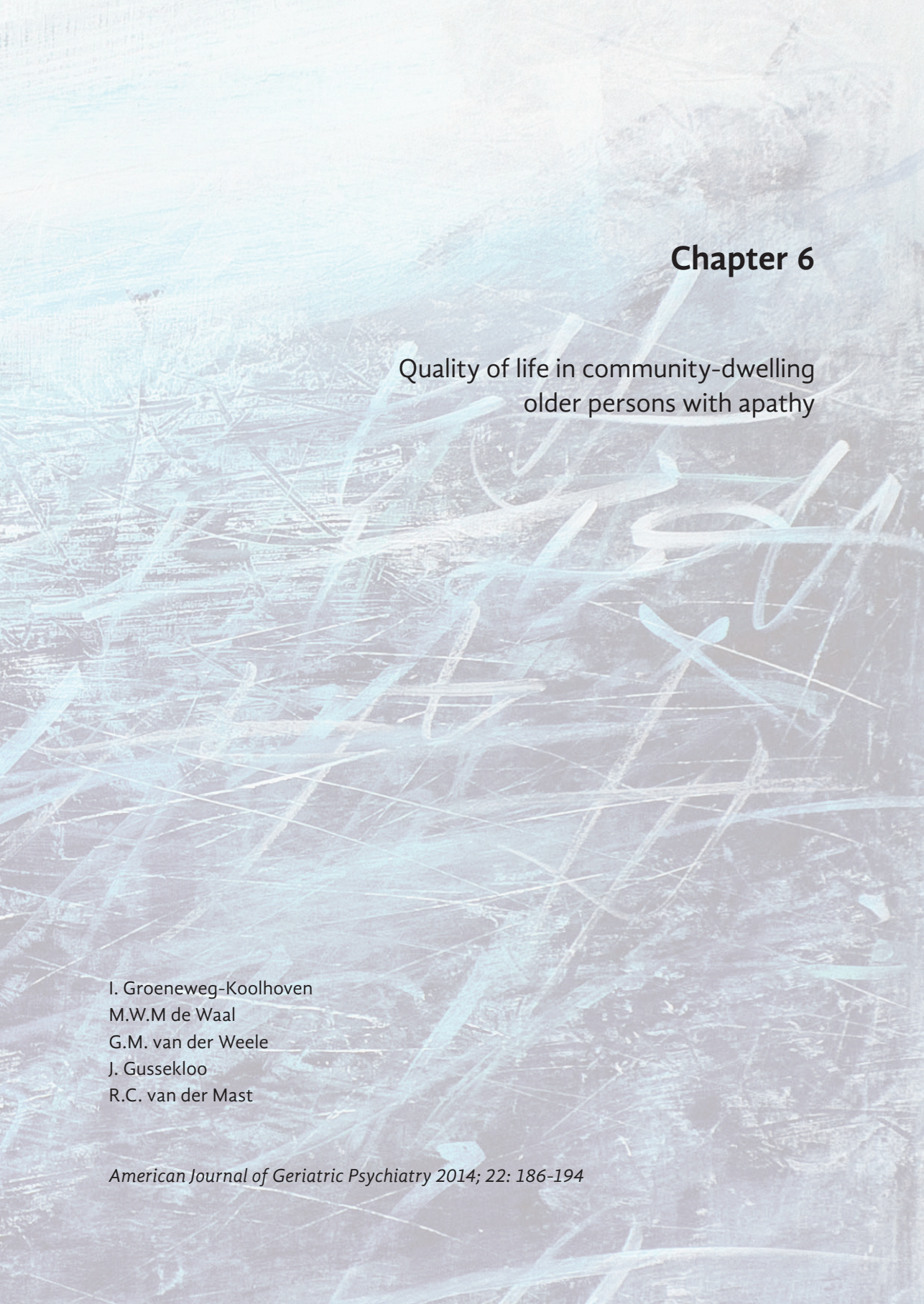
Note: Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.

¹Measured by the ankle-brachial index

²Measured by the Inventory of Depressive Symptomatology, 30 self-rating items

³AUDIT: Daily alcohol consumption





Chapter 6

Quality of life in community-dwelling older persons with apathy

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Abstract

Objective

To investigate the relationship between apathy and perceived quality of life in groups both with and without depressive symptoms or cognitive impairment.

Methods

We conducted a cross-sectional study comparing quality of life in older persons with and without apathy in 19 Dutch general practices. Participants were 1,118 older persons aged at least 75 years without current treatment for depression and a Mini-Mental State Examination score of at least 19. Perceived quality of life was determined using Cantril's Ladder for overall quality of life, EuroQol (EQ)-5D thermometer for subjective health quality, and De Jong-Gierveld Loneliness questionnaire for perceived loneliness. Apathy was assessed with the Apathy Scale.

Results

Of the 1,118 older persons, apathy was present in 122 (11%) of them. Overall, apathy was associated with having no work, lower level of education, presence of depressive symptoms, cognitive impairment, and decreased scores on all quality of life measures. Among the 979 (88%) older persons without depressive symptoms and cognitive impairment, apathy was present in 73 (7.5%) of them, showing similar associations as in the total population. In the 77 (7%) persons with cognitive impairment only, apathy was correlated to a lower score on the EQ-5D thermometer. However, in the 51 (5%) depressed persons without cognitive impairment, presence of apathy did not contribute to their decreased quality of life.

Conclusion

Apathy frequently occurred in community-dwelling older persons, also in the absence of depressive symptoms and cognitive impairment. In them, apathy contributed to the perception of a diminished quality of life in various aspects of daily life.

Introduction

Apathy is an important behavioral syndrome of several neuropsychiatric diseases, including depression and dementia, and is associated with reduced daily functioning,¹⁻⁵ caregiver distress^{6,7} and poor functional outcome.^{3,4,8-14} Consensus diagnostic criteria for apathy have been proposed¹⁵ and tested in clinical populations suffering from different neuropsychiatric diseases.¹⁶ Apathy is defined as a disorder of motivation that persists over time and is characterized by impairment of goal-directed behaviour, goal-directed cognitive activity, and/or emotions leading to functional impairments.^{2,15-19}

Of the few studies investigating apathy in community-based older populations,²⁰⁻²⁶ the prevalence of apathy ranged from 6 to 51%. The various risk factors for apathy include increasing age,^{20,23,26} although not consistently,²¹ having no partner and/or living alone,²¹ male gender,²⁶ cognitive impairment,^{21,27,28} depressive symptoms,^{21,22,26} and cardiovascular disease (CVD), including stroke and/or risk factors for CVD.^{22,29} Apathy has also been associated with decreased daily functioning^{20,21} and increased caregiver distress.²¹

It is often proposed that, in particular, caregivers of patients with apathy suffer more than the patients themselves due to the frequent presence of a lack of insight in apathy. However, few studies have investigated quality of life among older patients with apathy. One study found that among community-dwelling older persons who lived alone, apathy was not related to diminished quality of life,³⁰ which is in contrast to findings among clinical populations with dementia^{31,32} and Parkinson disease.³³

In the present cross-sectional study, we investigated whether apathy is associated with different aspects of perceived quality of life among community-dwelling older persons aged at least 75 years, both with and without comorbid depressive symptoms and cognitive impairment. Since depression and impaired cognition are well-known risk factors for both apathy and diminished quality of life, we were also interested in the additional effect of apathy on quality of life in this age group.

Methods

Subjects

This sub-study was part of the PROMODE (PROactive Management Of Depression in the Elderly) study. The primary aim of this randomized controlled trial was to investigate the (cost-) effectiveness of a combined screening and treatment program for older persons aged at least 75 years with depressive symptoms, in general practices in the Leiden region (the Netherlands).³⁴

The original study population consisted of 2,759 registered persons aged at least 75 years from 19 general practices (Figure 1). A total of 366 persons fulfilled the

following exclusion criteria: a life expectancy of no more than 3 months (n=22), current treatment for depression (n=141), loss of partner no more than 3 months ago (n=21), a diagnosis of dementia (n=114) and various other reasons (n=68). Of the remaining 2,393 persons who were invited to participate, 1,054 were non-responders (response rate 56%), and another 101 persons were excluded before/during the baseline interview due to current treatment for depression (n=37), decreased cognition (n=30), and other reasons (n=34). An additional 120 persons were excluded because of inadequate or missing data (Figure 1). This resulted in a total of 1,118 persons for inclusion in this sub-study on apathy and quality of life.

The Medical Ethical Committee of the Leiden University Medical Centre approved the study.

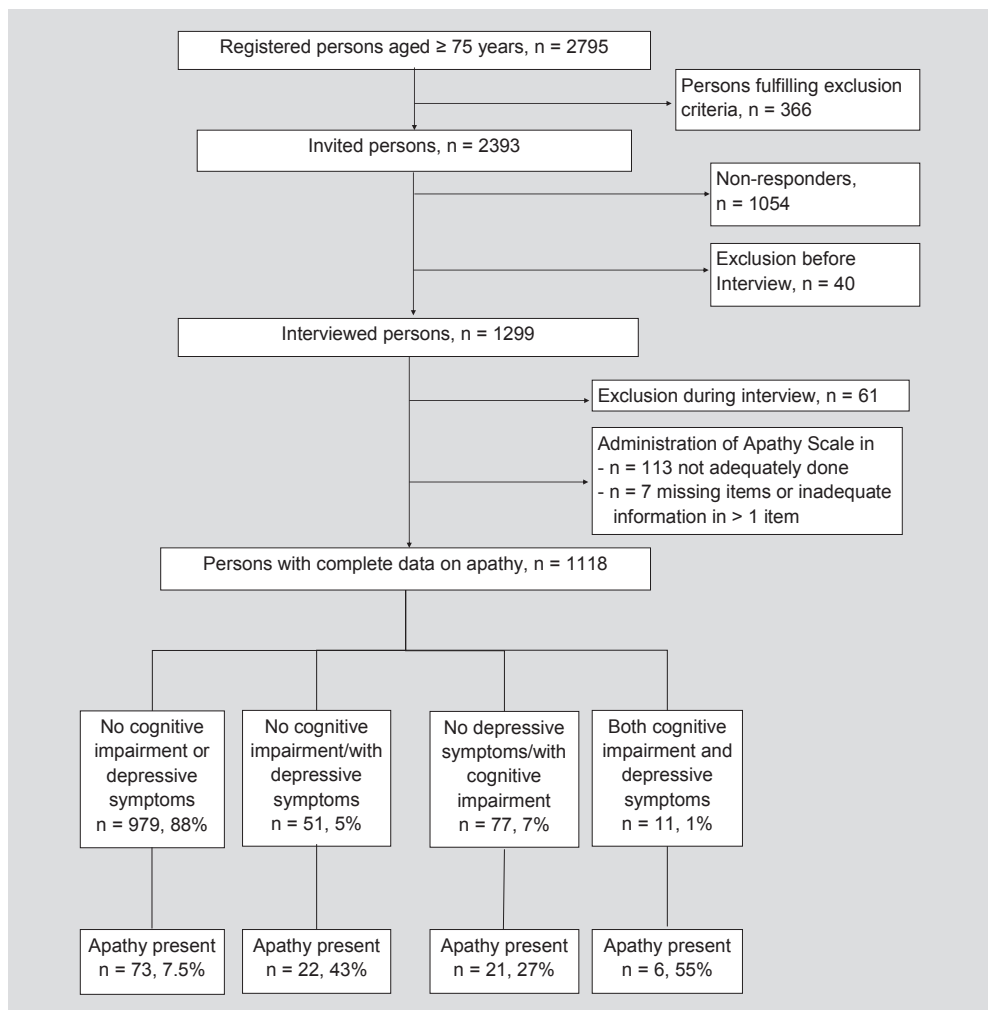


Figure 1. Flow chart PROMODE

Measures

Assessment of apathy

Apathy was assessed during a face-to-face interview using the Apathy Scale,³⁵ which is an abbreviation of the Apathy Evaluation Scale (AES),³⁶ and measures apathetic symptoms present in the last 4 weeks. The Apathy Scale, that has good inter-rater reliability and internal validity in patients suffering from Parkinson disease, consists of 14 items with four possible answers ranging from 0 to 3 points. Higher scores indicate more severe apathy.³⁵ A score of at least 14 points is indicative for the presence of apathy.^{11,35,37}

Assessment of perceived quality of life

To assess (various aspects of) quality of life the following three measures were used: 1) Cantril's Ladder,³⁸ a visual analogue scale (VAS) ranging from 1 (very bad) to 10 (excellent) for overall quality of life; 2) the EuroQol (EQ)-5D thermometer,³⁹ ranging from 0 to 100 for subjective health quality, that is a valid measure for determining subjective health quality;⁴⁰ and 3) the De Jong-Gierveld Loneliness questionnaire for perceived loneliness.⁴¹ This latter questionnaire consists of 6 items with a maximum score of six points; higher scores indicate more severe loneliness and a score of at least 2 indicates the presence of perceived loneliness.

Assessment of depressive symptoms and cognitive function

The 15-item Geriatric Depression Scale (GDS-15) was administered by an interviewer as a screening instrument for depressive symptoms.^{42,43} The GDS-15 ranges from 0 to 15 points, with higher scores indicating more depressive symptoms. A score of at least five points is considered indicative for the presence of clinically relevant depressive symptoms in older persons in general practice, with a sensitivity of 92% and a specificity of 81%.^{44,45}

Information on global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE), which is a screening instrument with a good inter-rater and test-retest reliability.⁴⁶⁻⁴⁸ Persons with an MMSE baseline score less than 19 points, indicating severe cognitive impairment, were excluded because this would compromise the reliability and validity of the measures used. A cut-off score of no more than 23 points was used for the presence of cognitive impairment.

Additional measures

For all persons, sociodemographic characteristics were obtained. Abuse of alcohol was defined as drinking at least 14 consumptions per week. Presence of anxiety was measured using the 7-item anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), with scores ranging from 0-21 points, and at least 8 points suggesting the presence of an anxiety disorder. This cut-off has a sensitivity and specificity of 90%.^{49,50}

Statistical analyses

Data are presented as numbers with percentages, medians with interquartile ranges (IQR), or means with standard deviations (SD) where appropriate. Using univariate logistic regression analyses, older persons with and without apathy were compared on all three quality of life measures, and on sociodemographic, neuropsychiatric, and clinical characteristics. Median scores of Cantril's Ladder and the EQ-5D thermometer were used as cut-off scores. Multivariate (logistic) regression analysis, thereby entering variables with a p-value < 0.05 as well as age and gender, was used to determine independent correlates for apathy. Multivariate analyses were performed in two models because of multicollinearity: one model with all variables except Cantril's Ladder (data presented) and one model with all variables except EQ-5D (only odds ratios and statistics of EQ-5D presented).

The relationship between apathy and quality of life measures in older persons with and without comorbid clinically relevant depressive symptoms ($\text{GDS-15} \geq 5$) and cognitive impairment ($\text{MMSE} \leq 23$) was investigated in four groups of older persons: 1) without both clinically relevant depressive symptoms and cognitive impairment, 2) with depression but without cognitive impairment, 3) without depression but with cognitive impairment, and 4) with both depression and cognitive impairment. Because the group of older persons with both depression and cognitive decline appeared to include only 11 persons, no further analyses regarding this subgroup were done, given the small sample size. Post hoc bivariate analyses within subgroups were computed with Pearson chi-square testing. Missing values were imputed with values representing a good Quality of Life (Cantril's ladder ≥ 8 and EQ-5D thermometer score ≥ 75).

A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 17.0 for Windows 7 (IBM).

Results

Sociodemographic and clinical characteristics

Table 1 presents the sociodemographic and clinical characteristics of the total study population ($n=1,118$). Mean age was 82 (SD: 5, range: 74-103) years. The median score on the Apathy Scale for the total population was 7 (IQR: 4-10), whereas 122 older persons (11%) had a score of at least 14, indicative for having apathy. A total of 62 (6%) persons had depressive symptoms based on a GDS score of at least 5, and 88 (8%) showed cognitive impairment based on an MMSE score of no more than 23.

Figure 1 shows the presence of apathy in the four subgroups of older persons. Among older persons without both clinically relevant depressive symptoms and cognitive impairment 73 (7.5%) showed apathy. In almost half of the older persons with depressive symptoms apathy was present, whereas apathy was present in more than one-fourth of older persons with cognitive impairment. Also, in more than half of the

older persons with both depressive symptoms and cognitive impairment, apathy was present. Because this latter subgroup comprised only 11 persons, no further analyses regarding this subgroup were done, given the small sample size.

Table 1. Sociodemographic and clinical characteristics of all 1,118 older persons

Sociodemographic characteristics		
Age in years, mean (SD, range)	82	(5, 74-103)
Female sex, n (%)	684	(61)
Income social security only, n (%)	141	(13)
No volunteer or paid work, n (%)	909	(81)
Living alone, n (%) ^a	641	(57)
Independent living, n (%) ^b	1074	(96)
Low level of education, n (%) ^c	333	(30)
Clinical characteristics		
Alcohol use > 14 drinks/week, n (%)	99	(9)
Quality of life		
Cantril's Ladder score, median (IQR)	8	(7-8)
Cantril's Ladder score < 8, n (%)	469	(42)
EQ-5D thermometer score, median (IQR)	75	(64-80)
EQ-5D thermometer score < 75, n (%)	518	(46)
De Jong-Gierveld Loneliness score, median (IQR)	1	(0-2)
De Jong-Gierveld Loneliness score ≥ 2, n (%)	338	(30)
Neuropsychiatric characteristics		
Apathy Scale score, median (IQR)	7	(4-10)
Apathy Scale score ≥ 14, n (%)	122	(11)
Geriatric Depression Scale score, median (IQR)	1	(0-2)
Geriatric Depression Scale score ≥ 5, n (%)	62	(6)
Hospital Anxiety Scale-Anxiety score, median (IQR) ^d	2	(0-3)
Hospital Anxiety Scale-Anxiety score ≥ 8, n (%)	48	(4)
Mini Mental Status Examination score, median (IQR)	8	(27-29)
Mini Mental Status Examination score ≥ 19 ≤ 23, n (%) ^e	88	(8)
<i>Notes:</i> Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate. ^a Being widowed/divorced; ^b not living in an elderly home or nursing home; ^c maximum of 6 years of schooling; ^d anxiety subscale of the Hospital Anxiety Depression Scale; ^e subjects with Mini-Mental Status Examination < 19 were excluded.		

Comparison of older persons with and without apathy

Using univariate analysis, Table 2 shows that older persons with apathy more often had a diminished perceived quality of life compared with those without apathy, as assessed with Cantril's Ladder, the EQ-5D thermometer, and the De Jong-Gierveld Loneliness questionnaire. Also, older persons with apathy more often showed clinically relevant depressive symptoms and cognitive impairment. Furthermore, older persons with apathy less often had volunteer or paid work, less often lived alone and independently, and more often had a low level of education. Using multivariate analysis, all quality of life measures and neuropsychiatric characteristics as well as having no (volunteer or paid) work and a low level of education appeared to be independent correlates for apathy (Table 2).

Comparison of subgroups of older persons with and without apathy

Figure 2 and table 3 show perceived quality of life according to the different measures used, in subgroups of older persons with and without apathy.

In the 979 older persons without both cognitive impairment and depressive symptoms, apathy was associated with a diminished quality of life as assessed with Cantril's Ladder the EQ-5D thermometer and the De Jong-Gierveld Loneliness questionnaire. Furthermore, among these older persons, apathy was associated less with often having volunteer (or paid) work and more often with having a low level of education.

Among the 77 older persons with cognitive impairment, the presence of apathy did not affect quality of life. Among the 51 older persons with depressive symptoms, quality of life was low and did not differ between older persons with and without apathy. Remarkably, in depressed older persons, the presence of apathy did not further affect their already poor quality of life.

For sensitivity analysis, all analyses for Table 3 were repeated using the continuous scores of Cantril's Ladder, the EQ-5D thermometer, and the De Jong-Gierveld Loneliness questionnaire; cut-off scores 5/6 and 6/7 for Cantril's Ladder, less than 70 and less than 80 for the EQ-5D thermometer, and at least 3 for the De Jong-Gierveld Loneliness questionnaire; and by excluding missing values for Cantril's ladder and the EQ-5D thermometer. These yielded similar results, except for the EQ-5D thermometer in the cognitively impaired older persons: a cut-off score less than 70 and excluding missing values showed a lower quality of life in the subgroup with apathy compared to the subgroup without apathy. Furthermore, in the depressed older persons a cut-off score 5/6 for Cantril's ladder showed a lower quality of life in the subgroup with apathy.

Table 2. Sociodemographic and clinical characteristics of older persons with and without apathy

	Apathy		Univariate analyses				Multivariate analyses			
	Absent n=996	Present n=122	OR	95% CI	Wald	p-value	OR	95% CI	Wald	p-value
Sociodemographic characteristics										
Age, Years, mean (SD)	82 (5)	82 (5)	1.0	(0.98-1.06)	1.298	0.255	0.98	(0.9-1.0)	0.431	0.511
Female sex, n (%)	610 (61)	74 (61)	1.0	(0.7-1.4)	0.9	0.9	0.7	(0.4-1.1)	2.988	0.084
No volunteer or paid work, n (%)	792 (80)	117 (96)	9.9	(3.1-31.6)	<0.005	<0.005	8.5	(2.6-27.8)	12.374	<0.005
Living alone, n (%)	561 (56)	80 (66)	1.5	(1.0-2.2)	0.052	0.052	0.8	(0.5-1.3)	1.007	0.316
Independent living, n (%) ^a	961 (97)	113 (93)	0.5	(0.2-0.98)	0.043	0.043	1.0	(0.4-2.5)	0.055	0.814
Low level of education, n (%) ^b	275 (28)	58 (48)	2.4	(1.6-3.5)	<0.005	<0.005	1.9	(1.2-2.9)	8.818	0.003
Clinical characteristics										
Alcohol use > 14 drinks/week, n (%)	87 (9)	12 (10)	1.2	(0.6-2.2)	0.601	0.601	-	-	-	-
Quality of life										
Cantril's Ladder score < 8, n (%)	392 (39)	77 (63)	2.8	(1.9-4.1)	<0.005	<0.005	1.7	(1.1-2.7)	5.785	0.016
EQ-5D thermometer score < 75, n (%)	439 (44)	79 (65)	2.5	(1.7-3.8)	<0.005	<0.005	1.7	(1.1-2.6)	5.305	0.021
De Jong-Gierveld Loneliness score ≥ 2, n (%)	273 (27)	65 (53)	3.0	(2.1-4.4)	<0.005	<0.005	2.1	(1.3-3.3)	13.376	<0.005
Neuropsychiatric characteristics										
Geriatric Depression Scale score ≥ 5, n (%)	34 (3)	28 (23)	8.4	(4.9-14.5)	<0.005	<0.005	4.8	(2.7-9.0)	25.393	<0.005
Hospital Anxiety Scale score ≥ 8, n (%) ^c	42 (4)	6 (5)	1.2	(0.5-2.8)	0.722	0.722	-	-	-	-
Mini Mental State Examination score ≥19 ≤ 23, n (%) ^d	61 (6)	27 (22)	4.4	(2.6-7.2)	<0.005	<0.005	2.3	(1.3-4.2)	7.478	0.006

Notes: Data are presented as numbers (percentages) or means (standard deviations) where appropriate;

Univariate and multivariate logistic regression analyses with df=1 for all variables, Odds ratios (OR) with 95% confidence intervals (CI), and Wald chi-square statistics;

^a not living in a residential home or nursing home;

^b maximum of 6 years of schooling;

^c Anxiety subscale of the Hospital Anxiety and Depression Scale;

^d subjects with Mini Mental Status Examination < 19 were excluded.

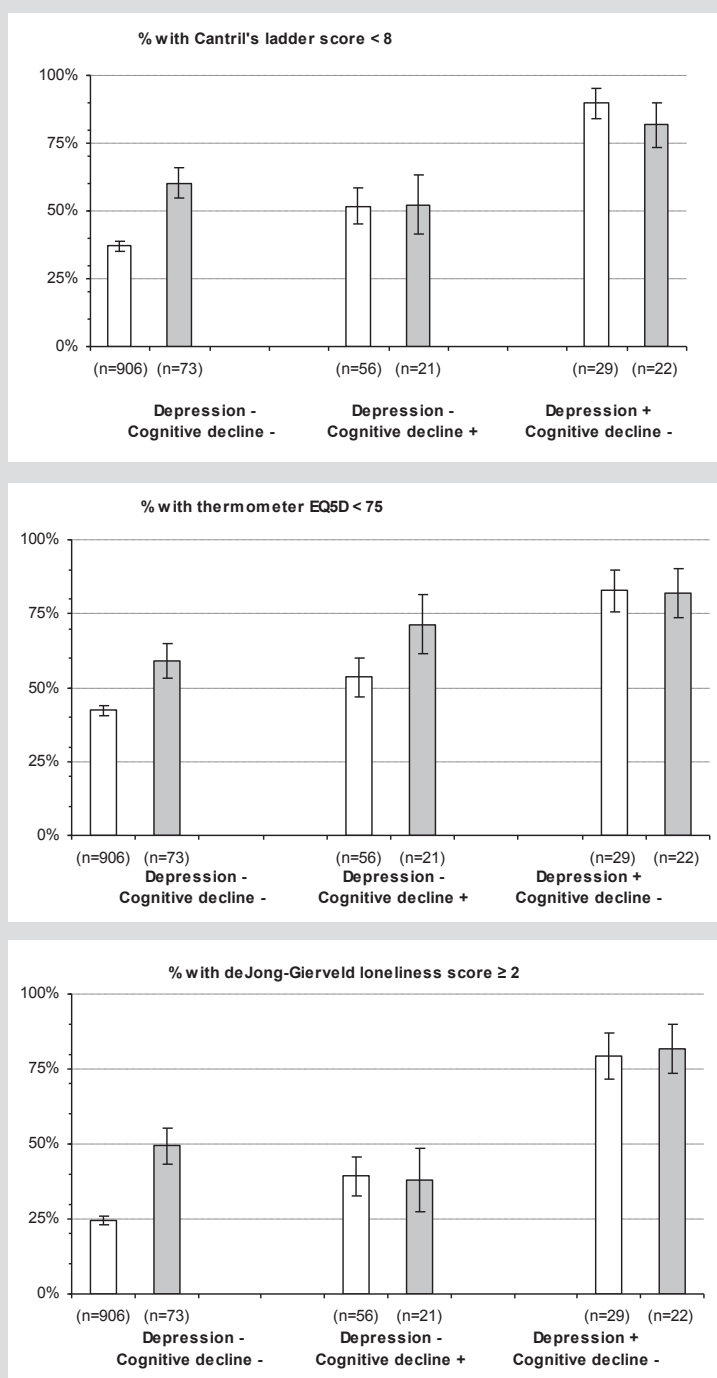


Figure 2. Poor quality of life in subgroups without apathy (white bars) and with apathy (grey bars), as measured with Cantril's ladder, thermometer EQ5D and deJong-Gierveld loneliness scale. Vertical lines in the bars represent the 95% confidence limits.

Table 3. Characteristics of apathy in older persons without cognitive impairment and with or without depressive symptoms.

	Depressive symptoms absent				Depressive symptoms absent				Depressive symptoms present			
	Apathy absent n=906	Apathy present n=73	Test ^a	p	Apathy absent n=56	Apathy present n=21	Test ^a	p	Apathy absent n=29	Apathy present n=22	Test ^a	p
Sociodemographic characteristics												
Age in years, mean (SD)	82 (5)	83 (5)	2.380	0.123	84 (5)	82 (5)	2.881	0.094	81 (5)	81 (5)	0.004	0.952
Female sex, n (%)	548 (61)	41 (56)	0.526	0.468	36 (65)	15 (71)	0.348	0.555	21 (72)	14 (64)	0.448	0.503
No volunteer or paid work, n (%)	713 (79)	70 (96)	12.294	0.000	52 (93)	20 (95)	1.508	0.219	24 (83)	21 (96)	4.023	0.045
Low level of education, n (%) ^b	277 (25)	32 (44)	12.471	0.000	36 (64)	13 (62)	0.037	0.847	9 (31)	8 (36)	0.160	0.689
Clinical characteristics												
Quality of life												
Cantril's Ladder score <8, n (%)	335 (37)	44 (60)	15.395	0.000	29 (52)	11 (52)	0.030	0.861	26 (90)	18 (82)	0.649	0.421
EQ-5D thermometer score <75, n (%)	383 (42)	43 (59)	7.602	0.006	30 (54)	15 (71)	2.005	0.157	24 (83)	18 (82)	0.008	0.930
DJG Loneliness score ≥2, n (%)	224 (25)	36 (49)	20.945	0.000	22 (39)	8 (38)	0.009	0.924	23 (79)	18 (82)	0.050	0.823
<i>Notes:</i> Data are presented as numbers (percentages) or means (standard deviations) where appropriate.												
^a Pearson Chi-square testing for dichotomous variables, and analysis of variance testing for continuous variables.												
^b maximum of 6 years of schooling												

Discussion

In this study, the presence of apathy among community-dwelling older persons was 11%. Although apathy in older persons often co-occurs with depressive symptoms and cognitive impairment, in 7.5% of the community-dwelling older persons, symptoms of apathy occurred in their own right without comorbid depressive symptoms or cognitive impairment. In these older persons, apathy was independently associated with decreased overall quality of life and subjective health quality and with increased perceived loneliness. Furthermore, apathy was associated with having no volunteer or paid work and a lower level of education.

Our results show that, contrary to the clinical impression, patients with apathy themselves also suffer from diminished quality of life, not only their caregivers as reported earlier.²¹ In older persons with depressive symptoms, quality of life was already low and the presence of apathy was not additionally associated with any of the quality of life measures. This may be related to a ceiling effect.

The results of this study are in contrast with the only other community-based study on quality of life in apathy, performed among 96 older persons aged at least 70 years who lived alone in a rural Japanese town.³⁰ In this latter study, remarkably, an extremely high prevalence of apathy (almost 98%) was found as assessed with the Apathy Scale, without any relationship to quality of life. Possibly, demographic and cultural differences had an impact on the very different outcomes compared to our study.

However, our results are very consistent with those of several studies among clinical populations including Alzheimer dementia and Parkinson disease, reporting the presence of apathy to be associated with a diminished quality of life,^{31,32,40,51,52} in particular in nursing home residents with a relatively good cognition (MMSE ≥ 18).⁵² Still, in these studies, it is unclear whether and to what extent apathy was also associated with diminished quality of life among persons without depressive symptoms or cognitive impairment (which we studied). Nevertheless, in two other studies among patients with Parkinson disease, apathy was independently associated with different dimensions on a self-report questionnaire assessing the impact of Parkinson disease on quality of life.^{33,53}

To our knowledge, this is the first study among a large population of community-dwelling older persons that investigated the relationship of apathy and perceived quality of life using various (self-rated) measures for quality of life, including overall quality of life according to a visual analogue scale, subjective health quality, and perceived loneliness. Apathy was assessed by trained research nurses using a validated apathy scale and analyzed in stratified samples of older persons with and without depressive symptoms and/or cognitive impairment.

This study has some limitations that need to be addressed. First, our study had a cross-sectional design, making it impossible to determine the temporal relationship of apathy

and quality of life and therefore to draw causal inferences. Also, selection bias may have occurred because older persons with more severe depression and serious cognitive impairment or dementia were lacking, because current treatment for depression, an MMSE score less than 19 points, or presence of a clinical diagnosis of dementia were exclusion criteria for the PROMODE study. Furthermore, due to the low response rate in the original study, the overall presence of apathy of 11% found in this study is probably an underestimation, because older persons with apathy more likely did not participate. In addition, we had no information on neurological disorders such as Parkinson disease and stroke or on objective health status and psychotropic medication use, which are all possible confounders for the association between apathy and our quality of life measures.

Although apathy is commonly a behavioral syndrome of various neuropsychiatric diseases, our study confirms that symptoms of apathy may also occur in their own right in community-dwelling older persons without depressive symptoms and cognitive impairment. This is an important finding because it has been shown, in mostly clinical studies, that apathy is related to decreased daily functioning, a lack of social contacts, and poor functional outcome.^{1-7,30} Evidence-based effective treatment of apathy, however, is largely lacking and the scarce studies that investigated the effect of pharmacologic⁵⁴⁻⁵⁶ and psychosocial interventions⁵⁷⁻⁶⁰ were all done in clinical populations with neuropsychiatric diseases such as depression and dementia. As far as we know, no studies have been done in community-dwelling older persons with apathy without neuropsychiatric comorbidity. Nonetheless, education and information about apathy and its possible concomitants may result in a better understanding of and coping with apathy, by the older persons themselves and their caregivers.

Conclusion

In community-dwelling persons aged at least 75 years with no comorbid depressive symptoms or cognitive impairment, apathy as a syndrome in its own right frequently occurred in over 7%. In those persons, apathy was associated with a perception of diminished overall quality of life and subjective health quality as well as increased loneliness. No additional effect of apathy on the already low quality of life in depressed older persons was found, whereas in older persons with merely cognitive impairment, apathy was only associated with diminished subjective health quality.

References

1. Steffens DC, Hays JC, Krishnan KR. Disability in geriatric depression. *Am J Geriatr Psychiatry* 1999;7:34-40.
2. Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry* 2001;158:872-877.
3. Landes AM, Sperry SD, Strauss ME. Prevalence of apathy, dysphoria, and depression in relation to dementia severity in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 2005;17:342-349.
4. Lam LC, Tam CW, Chiu HF, Lui VW. Depression and apathy affect functioning in community active subjects with questionable dementia and mild Alzheimer's disease. *Int J Geriatr Psychiatry* 2007;22:431-437.
5. Starkstein SE, Merello M. The Unified Parkinson's Disease Rating Scale: validation study of the mentation, behavior, and mood section. *Mov Disord* 2007;22:2156-2161.
6. Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, MacMillan A, Ketchel P, DeKosky ST. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc* 1998;46:210-215.
7. Thomas P, Clement JP, Hazif-Thomas C, Leger JM. Family, Alzheimer's disease and negative symptoms. *Int J Geriatr Psychiatry* 2001;16:192-202.
8. Resnick B, Zimmerman SI, Magaziner J, Adelman A. Use of the Apathy Evaluation Scale as a measure of motivation in elderly people. *Rehabil Nurs* 1998;23:141-147.
9. Duffy J. Apathy in neurologic disorders. *Curr Psychiatry Rep* 2000;2:434-439.
10. Yasuda N, Mino Y, Koda S, Ohara H. The differential influence of distinct clusters of psychiatric symptoms, as assessed by the general health questionnaire, on cause of death in older persons living in a rural community of Japan. *J Am Geriatr Soc* 2002;50:313-320.
11. van RR, Stuss DT, Ostrander L. Apathy: why care? *J Neuropsychiatry Clin Neurosci* 2005;17:7-19.
12. Hama S, Yamashita H, Shigenobu M, Watanabe A, Hiramoto K, Kurisu K, Yamawaki S, Kitaoka T. Depression or apathy and functional recovery after stroke. *Int J Geriatr Psychiatry* 2007;22:1046-1051.
13. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2006;77:8-11.
14. Lenze EJ, Skidmore ER, Dew MA, Butters MA, Rogers JC, Begley A, Reynolds CF, III, Munin MC. Does depression, apathy or cognitive impairment reduce the benefit of inpatient rehabilitation facilities for elderly hip fracture patients? *Gen Hosp Psychiatry* 2007;29:141-146.
15. Robert P, Onyike CU, Leentjens AF, Dujardin K, Aalten P, Starkstein S, Verhey FR, Yessavage J, Clement JP, Drapier D, Bayle F, Benoit M, Boyer P, Lorca PM, Thibaut F, Gauthier S,

- Grossberg G, Vellas B, Byrne J. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry* 2009;24:98-104.
16. Mulin E, Leone E, Dujardin K, Delliaux M, Leentjens A, Nobili F, Dessi B, Tible O, Aguera-Ortiz L, Osorio RS, Yessavage J, Dachevsky D, Verhey FR, Cruz Jentoft AJ, Blanc O, Llorca PM, Robert PH. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry* 2011;26:158-165.
 17. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci* 1991;3:243-254.
 18. van der Wurff FB, Beekman AT, Comijs HC, Stek ML, Hoogendijk WJ, Renes JW, Jonker C, Heeren T. [Apathy syndrome: a clinical entity?]. *Tijdschr Gerontol Geriatr* 2003;34:146-150.
 19. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry* 2008;79:1088-1092.
 20. Adams KB. Depressive symptoms, depletion, or developmental change? Withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *Gerontologist* 2001;41:768-777.
 21. Onyike CU, Sheppard JM, Tschanz JT, Norton MC, Green RC, Steinberg M, Welsh-Bohmer KA, Breitner JC, Lyketsos CG. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry* 2007;15:365-375.
 22. van der Mast RC, Vinkers DJ, Stek ML, Bek MC, Westendorp RG, Gussekloo J, de Craen AJ. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry* 2008;23:266-271.
 23. Mehta M, Whyte E, Lenze E, Hardy S, Roumani Y, Subashan P, Huang W, Studenski S. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *Int J Geriatr Psychiatry* 2008;23:238-243.
 24. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, Breitner JC, Steffens DC, Tschanz JT. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry* 2008;23:170-177.
 25. Maas DW, van der Mast RC, de Craen AJ. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry* 2009;24:1177-1184.
 26. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int Psychogeriatr* 2010;22:426-436.
 27. Tatsch MF, Bottino CM, Azevedo D, Hototian SR, Moscoso MA, Folquitto JC, Scalco AZ, Louza MR. Neuropsychiatric symptoms in Alzheimer disease and cognitively impaired, nondemented elderly from a community-based sample in Brazil: prevalence and relationship with dementia severity. *Am J Geriatr Psychiatry* 2006;14:438-445.

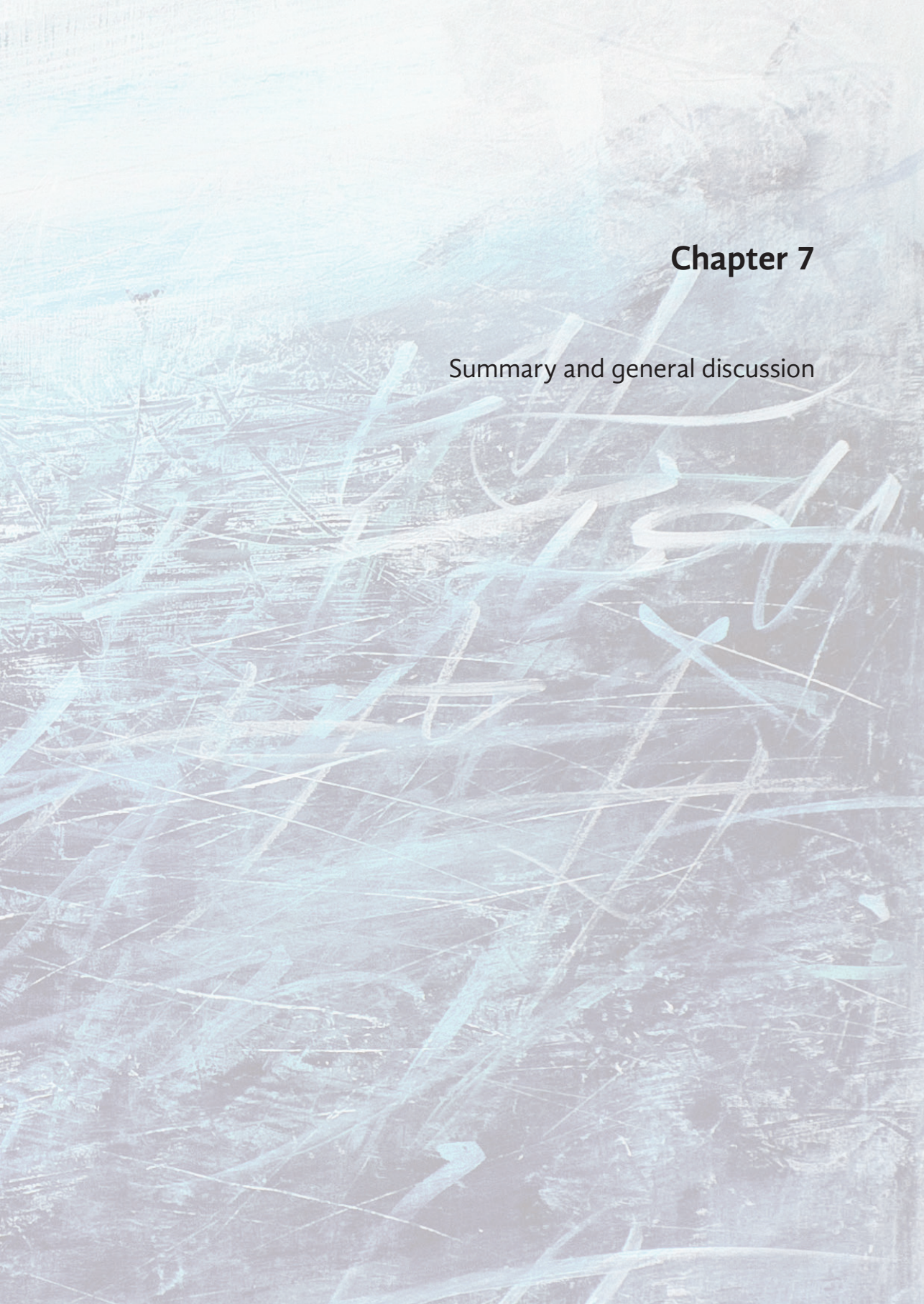
28. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr* 2010;22:819-829.
29. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - the Sydney Stroke Study. *Psychol Med* 2005;35:1707-1716.
30. Yamashita K, Iijima K, Kobayashi S. Relationship among activities of daily living, apathy, and subjective well-being in elderly people living alone in a rural town. *Gerontology* 1999;45:279-282.
31. Samus QM, Rosenblatt A, Steele C, Baker A, Harper M, Brandt J, Mayer L, Rabins PV, Lyketsos CG. The association of neuropsychiatric symptoms and environment with quality of life in assisted living residents with dementia. *Gerontologist* 2005;45 Spec No 1:19-26.
32. Bostrom F, Jonsson L, Minthon L, Londos E. Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease. *Alzheimer Dis Assoc Disord* 2007;21:150-154.
33. Oguru M, Tachibana H, Toda K, Okuda B, Oka N. Apathy and depression in Parkinson disease. *J Geriatr Psychiatry Neurol* 2010;23:35-41.
34. van der Weele GM, de Waal MW, van den Hout WB, van der Mast RC, de Craen AJ, Assendelft WJ, Gussekloo J. Yield and costs of direct and stepped screening for depressive symptoms in subjects aged 75 years and over in general practice. *Int J Geriatr Psychiatry* 2011;26:229-238.
35. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1992;4:134-139.
36. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991;38:143-162.
37. Pedersen KF, Alves G, Larsen JP, Tysnes OB, Moller SG, Bronnick K. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *Am J Geriatr Psychiatry* 2012;20:142-148.
38. Cantril H. The pattern of human concern. New Brunswick, NJ: Rutgers University; 1965.
39. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095-1108.
40. Bhattacharya S, Vogel A, Hansen ML, Waldorff FB, Waldemar G. Generic and disease-specific measures of quality of life in patients with mild Alzheimer's disease. *Dement Geriatr Cogn Disord* 2010;30:327-333.
41. van Tilburg TG, de Jong GJ. [Reference standards for the loneliness scale]. *Tijdschr Gerontol Geriatr* 1999;30:158-163.
42. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull* 1988;24:709-711.

43. Wancata J, Alexandrowicz R, Marquart B, Weiss M, Friedrich F. The criterion validity of the Geriatric Depression Scale: a systematic review. *Acta Psychiatr Scand* 2006;114:398-410.
44. Lyness JM, Noel TK, Cox C, King DA, Conwell Y, Caine ED. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Arch Intern Med* 1997;157:449-454.
45. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. *Int J Geriatr Psychiatry* 1999;14:858-865.
46. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
47. Cockrell JR, Folstein MF. Mini-Mental State Examination (MMSE). *Psychopharmacol Bull* 1988;24:689-692.
48. Mackin RS, Ayalon L, Feliciano L, Arean PA. The sensitivity and specificity of cognitive screening instruments to detect cognitive impairment in older adults with severe psychiatric illness. *J Geriatr Psychiatry Neurol* 2010;23:94-99.
49. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-370.
50. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52:p 69-77.
51. Yeager CA, Hyer L. Apathy in dementia: relations with depression, functional competence, and quality of life. *Psychol Rep* 2008;102:718-722.
52. Gerritsen DL, Jongenelis K, Steverink N, Ooms ME, Ribbe MW. Down and drowsy? Do apathetic nursing home residents experience low quality of life? *Aging Ment Health* 2005;9:135-141.
53. McKinlay A, Grace RC, Dalrymple-Alford JC, Anderson T, Fink J, Roger D. A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. *Parkinsonism Relat Disord* 2008;14:37-42.
54. Padala PR, Burke WJ, Bhatia SC, Petty F. Treatment of apathy with methylphenidate. *J Neuropsychiatry Clin Neurosci* 2007;19:81-83.
55. Corcoran C, Wong ML, O'Keane V. Bupropion in the management of apathy. *J Psychopharmacol* 2004;18:133-135.
56. Berman K, Brodaty H, Withall A, Seeher K. Pharmacologic treatment of apathy in dementia. *Am J Geriatr Psychiatry* 2012;20:104-122.
57. Alexopoulos GS, Raue P, Arean P. Problem-solving therapy versus supportive therapy in geriatric major depression with executive dysfunction. *Am J Geriatr Psychiatry* 2003;11:46-52.
58. Staal JA, Sacks A, Matheis R, Collier L, Calia T, Hanif H, Kofman ES. The effects of Snoezelen (multi-sensory behavior therapy) and psychiatric care on agitation, apathy, and activities

of daily living in dementia patients on a short term geriatric psychiatric inpatient unit. *Int J Psychiatry Med* 2007;37:357-370.

59. Verkaik R, van Weert JC, Francke AL. The effects of psychosocial methods on depressed, aggressive and apathetic behaviors of people with dementia: a systematic review. *Int J Geriatr Psychiatry* 2005;20:301-314.
60. Brodaty H, Burns K. Nonpharmacological management of apathy in dementia: a systematic review. *Am J Geriatr Psychiatry* 2012;20:549-564.



The background of the page is an abstract composition of numerous overlapping brushstrokes. The strokes are primarily in shades of light blue and white, set against a darker, muted blue-grey background. The strokes vary in length, thickness, and direction, creating a sense of movement and texture. Some strokes are straight and diagonal, while others are curved or horizontal. The overall effect is a layered, painterly texture that fills the entire page.

Chapter 7

Summary and general discussion

Summary and general discussion

Background

The main objective of the work presented in this thesis was to investigate different aspects of apathy, as a distinct clinical syndrome, in older persons with and without concurrent depression. Although the concept of apathy has existed for centuries, its meaning has changed over time. Nowadays, apathy as a distinct clinical syndrome indicates an important loss of motivation that interferes with daily functioning and is manifested by diminished goal-directed behavior, goal-directed cognition and reduced emotional display.^{1,2} Apathy as a distinct clinical syndrome interferes with quality of life and is associated with diverse negative health outcomes, including higher mortality and less benefit derived from rehabilitation and treatment of depression.²⁻⁸

In late-life depression, apathy may be very prominent; nevertheless, knowledge on apathy as a distinct, clinically relevant behavioral syndrome in depressed older persons is scarce. In this thesis, apathy in both depressed and non-depressed older persons was broadly investigated: the main results are summarized and discussed below in the context of previous research. Then, methodological issues related to the study of apathy in old age are addressed, clinical implications are discussed, and some recommendations are made for future research.

Summary of the results

Subtypes of apathy

According to the diagnostic criteria, apathy as a disorder of motivation is characterized by symptoms in three different life domains: behavioral, cognitive, and emotional.⁹ Distinct symptom profiles of apathy may indicate different apathy subtypes that are related to specific characteristics and, therefore, require distinct treatment approaches.^{10,11} Such subtypes of apathy cannot be identified using (total) scale scores of a measurement scale.¹² Therefore, we used the data-driven technique Latent Class Analysis (LCA) to identify groups of persons (Classes) based on distinct symptom profiles in the general population-based PROMODE cohort of 122 older persons with apathy (**Chapter 2**). Using LCA, we were able to identify three classes. Further exploration of the characteristics across these three classes showed that persons in Class 2 had more serious apathy and depression, higher alcohol consumption, and more often lived alone, compared to Class 1 and Class 3. On the other hand, Class 3 showed the lowest level of education, the lowest Mini-Mental State Examination (MMSE) score, and the highest quality of life, compared to the other two Classes. However, no distinct apathy subtypes could be identified, since only the level of education and severity of apathy were independent predictors for Class membership.

Apathy in late life

Although apathy often co-occurs with depression, there is increasing evidence that apathy may be a distinct, clinically relevant behavioral syndrome, independent of depression and, possibly, with a different etiology from depression.^{2,13-17} In **Chapter 3** we describe the results of the baseline cross-sectional study among depressed and non-depressed older persons in the NESDO study; we showed that clinically relevant apathy was present in 75% of the depressed and in 25% of the non-depressed older persons. Depressed and non-depressed older persons with apathy differed from each other, since severity of depressive symptoms was associated with apathy in depressed persons, whereas higher levels of C-reactive protein (CRP) were associated with apathy in non-depressed older persons. Male gender and having had less education were independently associated with the presence of clinically relevant apathy in both depressed and non-depressed older persons.

To further study the presence and impact of apathy in depressed older persons, **Chapter 4** investigates the incidence, course and several predictive factors of apathy at 2-year follow-up among depressed older persons in the NESDO study. Baseline severity of apathy, but not of depression, predicted the severity and persistence of apathy, as well as poor recovery of depression at follow-up. Furthermore, we found that worse global cognitive functioning at baseline, but not severity of depression, predicted the 2-year incidence of apathy in depressed older persons.

Although depression in younger adults is also often accompanied by apathy, studies show that depression in older persons may differ in its phenomenology from depression in younger persons. This may especially be the case for the presence of (clinically relevant) apathy, which is more prevalent in late-life depression.¹⁸⁻²¹ Therefore, in **Chapter 5** we examined the presence and comorbidities of clinically relevant apathy in older compared to younger depressed persons. It was shown that, of the 363 older depressed persons, 269 (74%) had clinically relevant apathy compared to 116 (54%) of the 217 younger depressed persons. Although older depressed persons more often showed apathy, the same associated risk factors were largely found in both age groups; the exception was for smoking, which was specifically associated with apathy in older depressed persons. In the total group of both younger and older depressed persons, apathy was independently associated with higher age, male gender, and the presence of more severe depression.

Burden of apathy

Apathy is associated with poor functional outcome, chronicity, and increased overall mortality. Although apathy also gives rise to increased distress for the caregivers, it is largely unknown to what extent apathy places a burden on the patients themselves.

Chapter 6 presents the results of our study examining perceived quality of life in relation to clinically relevant apathy in 1118 community-dwelling older persons in the PROMODE study. Apathy was found in 122 (11%) of these community-dwelling older persons. In 73 of these older persons with apathy, without depressive symptoms and cognitive impairment, apathy was associated with a diminished quality of life in various aspects of daily life. Moreover, older persons with both apathy and cognitive impairment experienced decreased subjective health quality compared to those without apathy. In depressed persons, apathy had no additional negative effect on the already low quality of life.

General Discussion

Concept of apathy

The concept 'Apathy' is not yet fully clarified. For a long time, apathy was considered to be merely a symptom of diverse neuropsychiatric disorders. Only in the last 30 years has apathy been increasingly acknowledged and investigated as a distinct, clinically relevant syndrome. However, controversy remains as to whether apathy should primarily be seen as a symptom of a neuropsychiatric disorder, including late-life depression, or also as a syndrome in its own right. At the same time, when apathy is very prominent and shows a cluster of different (motivational) symptoms (as described e.g. by Marin), it seems appropriate to consider apathy as a distinct clinical syndrome.²² Another problem is that, due to the lack of formal diagnostic criteria for apathy, clinicians and researchers fail to consistently use the same terminology; e.g. terms such as "flattened affect," "amotivation," or "avolition" are sometimes used when they may possibly refer to apathy. Another important area of debate focuses on the differentiation between apathy and depression. Literature shows that in different clinical populations apathy can be present in the absence of depression, but then lacking mood-related symptoms.^{7,23-25} Supporting evidence for the existence of apathy as a distinct syndrome includes different pathophysiology, etiologies and risk factors for apathy compared with depression. Neuropathologic and neuroimaging studies link apathy to abnormalities in specific regions of the frontal lobe, anterior cingulate gyrus and basal ganglia, whereas depression is particularly associated with abnormalities in the frontal-striatal and subcortical limbic circuits.^{26,27} Neurochemically, apathy reflects a dysfunction of fronto-subcortical projection systems, including monoaminergic, cholinergic, glutamatergic, and GABAergic pathways, whereas depression is supposed to reflect serotonergic deficits or a dopamine and norepinephrine imbalance.^{27,28}

Diagnosis of apathy

Marin was the first to conceptualise apathy as a distinct behavioral syndrome consisting of diminished or absence of motivation and drive, as the core feature that was noticeably expressed in decreased goal-directed behavior, cognition and/or emotion.^{22,29} He

stated that the lack of motivation should not be attributed to emotional distress, intellectual impairment, or diminished level of consciousness.²² In 2001, Starkstein et al. modified the diagnostic criteria formulated by Marin, by omitting the necessity of an absence of emotional distress and intellectual impairment. On the other hand, they included the following requirements: *“The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning”* and *“The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication)”*.²⁹ A few years later they additionally stated *“...the symptoms should be present for at least 4 weeks during most of the day”*.³⁰ Following Starkstein et al., a task force consisting of international experts from Europe, America and Australia formulated consensus criteria for apathy. In these consensus criteria the necessity to have at least one symptom present in each of the three domains (behavior, cognition, emotion) was changed to at least one symptom in at least two of the three domains. Additionally, the symptoms should not exclusively be explained by or due to physical or motor disabilities.⁹ Although these consensus criteria for apathy were validated in different clinical populations (Alzheimer disease, Parkinson disease, major depression, schizophrenia, etc.), until now they have not been formally acknowledged.³¹ In addition, apathy as a distinct clinical syndrome has hardly been described in textbooks and is not included in the DSM-5. Apathy is mentioned in the DSM-5 only under clinically relevant behavioral disturbances as a specifier of several neurocognitive disorders.³²

Assessment of apathy

In order to assess symptoms and severity of apathy, Marin et al. (1991) developed the Apathy Evaluation Scale (AES).³³ Although the inter-rater and test-retest reliability, as well as its ability to discern apathy from depression are good, no consistent threshold values for the AES are known to determine clinically relevant apathy.³⁴ Subsequently, in a number of clinical populations with Parkinson disease, Alzheimer disease, stroke, and major depressive disorders, other measurement scales including the Dementia and Apathy Interview Rating scale, the Apathy Inventory, and the Lille Apathy Rating Scale were developed to assess, characterize and quantify apathy as a distinct syndrome.³⁵⁻³⁷ Only for the Apathy Scale (derived from the AES) was a threshold score determined for the presence of clinically relevant apathy (in patients with Parkinson disease). To date, the Apathy Scale has been used in clinical studies among older persons with Parkinson disease, Alzheimer disease, post-stroke patients, Huntington disease, major depression, and chronic low back pain, as well as in community-based studies.^{29,38-44}

Other instruments such as the the Neuropsychiatric Inventory (NPI), the Brief Psychiatric Rating Scale, and the Frontal Systems Behavior Scale, include only a single item for the assessment of apathy, which makes it impossible to decide whether apathy is a clinically important behavioral syndrome.^{27,34}

The Apathy Evaluation Scale,³³ the Apathy Scale,³⁸ the Apathy Inventory³⁷ and the Lille

Apathy Rating Scale³⁶ were all recommended by the Task Force for assessment of apathy, showing adequate psychometric properties. However, all these instruments lack proper validation against external criteria, which also applies to the Apathy Scale.^{27,34} Also, this diversity of instruments does not allow proper comparisons of different studies on apathy.

With this dilemma in mind, we sought the best possible way to answer our research questions. We found that the Apathy Scale was the most appropriate measure to assess apathy, giving the fact that it was recommended by the international Task Force, showed fairly good psychometric properties in different clinical populations and, importantly, has a known threshold score ≥ 14 for apathy as a distinct, clinically relevant behavioral syndrome.^{29,38,39,45}

Subtypes of apathy

Decreased motivation, interests, action initiation and emotional reactivity are all dimensions of apathy, in which the lack of motivation is the core feature, which may relate to internal (self-conducted behavior) or external stimulation.⁹ Moreover, because multiple different prefrontal-basal ganglia circuits may underlie these various dimensions, apathy may differ in its clinical expression. In addition, neurochemically, apathy reflects dysfunction of different fronto-subcortical projection systems (including monoaminergic, cholinergic, glutamatergic, and GABAergic pathways). Also, different treatment approaches may then be needed, as was found in studies among various clinical populations.²⁷ Thus, apathy is probably best regarded as a heterogeneous disorder with (possibly) numerous subtypes.^{27,46} Until now, however, no studies have focused on the identification of clinical subtypes of apathy. Our study in an older community-based sample with apathy (from the PROMODE study) did not reveal any subtype of apathy using the Apathy scale. Although 3 classes emerged using LCA, no associated differences were found between these classes, indicating that the Apathy scale measures a rather homogeneous concept. However, older persons with more severe depression and serious cognitive impairment (thus suffering from more severe apathy) were excluded from this study, which may have resulted in insufficient heterogeneity to detect distinct subtypes of apathy.

Apathy in late life

In 25% of the non-depressed older persons apathy was present, which is in line with other studies among healthy community-dwelling older persons that reported an occurrence of 1-27%.^{3,14,15,47-49} In addition, apathy occurred in 75% of the depressed older persons, which is within the wide range of prevalence (38-96%) reported in the literature. These differences in prevalence rates are probably due to different criteria and measurement instruments used to assess apathy.^{2,3,14,15,48-51} The three studies that reported prevalence rates of apathy of 70-96% comprised older persons

suffering from more severe depression, whereas apathy was mostly assessed with measurement instruments specifically designed to quantify apathy.^{23,50,51} One study excluded depressive persons who did not use antidepressants,⁵⁰ another study included only inpatients who were admitted to an acute psychiatric ward⁵¹ and the third study used high scores on the Hamilton Rating Scale for Depression (HAM-D) and the AES to determine the presence of apathy.²³ The studies that reported apathy prevalence rates in the lower range (i.e. 38–55%) in persons with depressive symptoms used more general screening instruments (e.g. the NPI and the GDS). Further, these studies were performed in community-based populations and populations with Alzheimer's disease; and apathy was also assessed in persons with comorbid depressive disorders according to the DSM-IV.^{7,14,45,49} Another study in older persons with major depression showed an apathy prevalence rate of 38%. However, this relatively low prevalence rate might be explained by the selection of older persons with less severe depression and less comorbidity, because persons with psychotic depression, those with comorbid severe medical and neurologic disorders, and those who used certain medications and drugs were excluded.¹⁶ Since our study population consisted of both inpatients and outpatients, mostly suffering from a major depression, and because apathy was assessed using a well-validated measurement instrument, and the prevalence rate of 75% for apathy is in line with the higher prevalence rates mentioned above,⁵⁰ we believe that our prevalence rates are reliable and representative for a depressed sample of older adults.

Apathy may be associated with different risk factors in non-depressed compared to depressed older persons,^{7,24,49,52,53} which suggests a different etiology for apathy in both populations. In our study we found that male gender and level of education were independent correlates of apathy in both depressed and non-depressed older persons,^{3,48,49} whereas higher CRP levels were particularly associated with apathy in non-depressed persons. Higher CRP levels are associated with more severe apathy, also in community-dwelling older persons without a history of cardiovascular disease.¹⁵ At old age, these higher CRP levels may reflect low-grade inflammation that, like apathy, is associated with (subclinical) underlying cardiovascular disease.^{54,55} As hypothesized by Dantzer et al., this low-grade inflammation may result in a cluster of symptoms including somnolence, loss of energy, malaise, and diminished interest in activities, that resemble symptoms of apathy,⁵⁶ and may be associated with underlying atherosclerosis that leads to future vascular events. Indeed, it was shown that symptoms of apathy, but not of depression, were a risk factor for cardiovascular disease in community-based older persons.^{15,54,57}

Cognitive decline is also associated with apathy in older persons, in that apathy is more often present when cognition decreases. Apathy predicts cognitive decline in the future,^{7,48,58} whereas, at the same time, cognitive decline may predict the occurrence

of apathy. This was shown by our finding that worse global cognitive functioning at baseline (and not severity of depression) predicted the 2-year incidence of apathy, but only in depressed older persons. The question remains whether apathy is a consequence, or a predictor, or both, of cognitive decline.³ It is essential to understand the direction of this relationship, since this can have important implications for the management and treatment of both apathy and cognitive decline.

Apathy is also a well-known symptom of depression in younger depressed persons,¹⁸⁻²⁰ and we have shown that not only in older but also in younger depressed persons, apathy can be very prominent, presenting itself as a distinct behavioral syndrome. Although apathy was associated with different risk factors in late life, compared to early life, both in younger and older depressed persons clinically relevant apathy was only associated with depression severity, indicating more severe depression.

It is suggested that older persons with apathy suffer less than their caregivers do; this may be due to lack of insight into their illness (anosognosia) whereby they may not experience a diminished quality of life.^{59,60} However, several clinical studies have shown that this is not true and that older persons with apathy do indeed experience diminished quality of life,⁶¹⁻⁶⁵ as we also found in our community-based study. It is possible that the absence of drive and motivation impedes these persons from expressing their experienced decline in quality of life.

Further, the presence of apathy appeared to have a negative effect on the recovery and prognosis of (underlying) depression, and was also associated with chronicity,^{4,16,50,66,67} and a more complicated course of depression, which leads to greater functional impairments, particularly at old age. This strengthens the need to distinguish between clinically relevant apathy and depression, and to pay appropriate attention to the treatment of both, thereby hopefully ameliorating both the course and prognosis.

Methodological considerations

Study designs

For the studies described in this thesis, data were used from two observational prospective cohort samples (the NESDO and NESDA studies) and from a randomized controlled trial sample (the PROMODE study). All participants from the PROMODE sample were recruited in a general healthcare setting, giving us the opportunity to investigate apathy in an older rather heterogeneous community-dwelling population. In NESDO, both older inpatients and outpatients were included from both general health care and mental health care, consisting of depressed and non-depressed older persons; this enabled us to examine apathy and its course in both a depressed and non-depressed older sample. This is unique since little is known about apathy in combination with depressive disorder at old age. Most studies until now examined apathy cross-sectionally and particularly in clinical populations suffering from dementia, stroke and

Parkinson disease, with and without comorbid depressive symptoms.^{1,25,29} In addition, we had the opportunity to use data from the NESDA study that allowed us to examine possible differences in the presence and associating comorbidities of apathy between older depressed and younger depressed persons.

General strengths and limitations

The studies described in this thesis need to be interpreted in the light of certain strengths and limitations.

The use of a large community-dwelling population from the PROMODE study made it possible to examine quality of life in relation to the presence of apathy, which has only been examined within clinical populations,^{61,64,68} and to investigate possible subtypes of apathy. A major strength of the NESDO study was the follow-up of the older persons, which enabled us to investigate the incidence and course of apathy in older persons with depression. In addition, in our population, both depression and apathy were diagnosed using well-established validated measures.

An important limitation of the studies described in this thesis is that no formal diagnostic criteria exist for apathy as a distinct behavioral syndrome, which makes comparison with other studies difficult. Secondly, since symptoms of apathy and depression may overlap, especially with regard to motivational symptoms, underestimation and overestimation of apathy or depression may have occurred. However, the Apathy Scale has shown good discriminant validity between apathy and depression^{29,38,45} and the overlap of items in the Apathy Scale and the Inventory for Depressive Symptomatology (IDS) was low. Thirdly, most studies in this thesis have a cross-sectional design, which prevented us from drawing causal inferences. Fourthly, an important phenomenon in cohort studies, particularly among older persons, is the degree of attrition. In the NESDO study, almost 25% of the persons were lost after 2-year follow-up due to death, and refusal or inability to further participate, mainly among participants who at baseline already showed severe physical and/or neuropsychological morbidity. This may have led to an underestimation of the presence of apathy at follow-up, since those with apathy were most likely to drop out. However, compared to other studies among older persons, our attrition was not considered to be high.⁶⁹ Fifthly, persons with more severe apathy might not have participated because of a lack of motivation, resulting in the inclusion of a less heterogeneous group of older persons with only mild to moderate apathy, missing associating factors with apathy and limiting generalizability to persons with more severe apathy.

Clinical implications

Back to the case report

Mr. A suffered from depression with comorbid apathy that persisted after adequate treatment of the depression.^{2,16} After admission to our hospital, the psychotic depression

Mr. A. suffered from was adequately treated with nortriptyline and lithium carbonate. However, he still showed hardly any spontaneous speech, almost never talked, lacked all initiative, sat on the couch all day doing nothing, was generally inactive, and showed no social engagement without being bothered by it. Our conclusion was that he (still) suffered from clinically relevant apathy. Although no evidence-based treatment is known for apathy, a possible treatment option is methylphenidate.^{27,70} Therefore, we treated the patient with low doses (5 mg) methylphenidate 2 times/day and, within 1 week, he showed an increase in motivational behavior (went cycling spontaneously) and was more responsive to his environment. The improvement continued and, after a year, the methylphenidate could be stopped without reoccurrence of the apathy. He was very happy about his improvement in daily functioning and stated that he had indeed been bothered by his inactivity.

It is known that caregivers of patients with apathy experience great distress, while patients themselves do not always seem to feel apathy as an important burden.^{49,71,72} However, this patient was bothered by being apathetic, even though he did not complain about it at that time, possibly due to lack of motivation and drive.

Thus, although Mr. A was adequately treated for his depression, the apathy remained and required a different treatment approach. There is no specific pharmacologic agent known to be effective in the treatment of apathy, the most frequently used pharmacologic agents in older persons with apathy include dopaminergic antiparkinson agents, acetylcholinesterase inhibitors for Alzheimer disease, and psychostimulants.²⁷ However, there is insufficient evidence for any pharmacological treatment to improve apathy since randomized controlled studies with apathy as primary outcome are lacking.⁷⁰

Directions for future studies

The aim of the work described in this thesis was to investigate different aspects of apathy - as a distinct clinical syndrome - in older persons with and without co-occurring depression. Clear diagnostic criteria are needed to help clinicians recognize and diagnose the presence of clinically relevant apathy and to differentiate this syndrome from depression. Some researchers have hypothesized that apathy can be divided into different domains,^{36,73,74} thereby indicating disease-specific variations in the clinical presentation of apathy in certain populations; however, this line of investigation requires further research. Since apathy as a clinically relevant syndrome probably needs a different treatment approach, future studies should not only focus on (early) diagnosis and risk factors, but also on the treatment of apathy. Until now, no adequate pharmacotherapy has been approved for apathy and randomized controlled trials are needed to study the efficacy of pharmacotherapy and behavioral treatment programs for apathy in different clinical populations.

References

1. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - the Sydney Stroke Study. *Psychol Med.* 2005;35:1707-1716.
2. Yuen GS, Bhutani S, Lucas BJ, et al. Apathy in Late-Life Depression: Common, Persistent, and Disabling. *Am J Geriatr Psychiatry.* 2015;23:488-494.
3. Brodaty H, Altendorf A, Withall A, Sachdev P. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *Int Psychogeriatr.* 2010;22:426-436.
4. Levkovitz Y, Sheer A, Harel EV, et al. Differential effects of deep TMS of the prefrontal cortex on apathy and depression. *Brain Stimul.* 2011;4:266-274.
5. Lenze EJ, Skidmore ER, Dew MA, et al. Does depression, apathy or cognitive impairment reduce the benefit of inpatient rehabilitation facilities for elderly hip fracture patients? *Gen Hosp Psychiatry.* 2007;29:141-146.
6. Lavretsky H, Zheng L, Weiner MW, et al. Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. *Am J Psychiatry.* 2010;167:589-597.
7. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 2006;77:8-11.
8. Resnick B, Zimmerman SI, Magaziner J, Adelman A. Use of the Apathy Evaluation Scale as a measure of motivation in elderly people. *Rehabil Nurs.* 1998;23:141-147.
9. Robert P, Onyike CU, Leentjens AF, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry.* 2009;24:98-104.
10. Pedersen KF, Alves G, Larsen JP, Tysnes OB, Moller SG, Bronnick K. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *Am J Geriatr Psychiatry.* 2012;20:142-148.
11. Starkstein SE. Apathy in Parkinson's disease: diagnostic and etiological dilemmas. *Mov Disord.* 2012;27:174-178.
12. Nandi A, Beard JR, Galea S. Epidemiologic heterogeneity of common mood and anxiety disorders over the lifecourse in the general population: a systematic review. *BMC Psychiatry.* 2009;9:31.
13. Maas DW, van der Mast RC, de Craen AJ. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *Int J Geriatr Psychiatry.* 2009;24:1177-1184.
14. van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *Int J Geriatr Psychiatry.* 2008;23:266-271.
15. Ligthart SA, Richard E, Fransen NL, et al. Association of Vascular Factors With Apathy in Community-Dwelling Elderly Individuals. *Vascular Factors and Apathy. Arch Gen Psychiatry.* 2012;69:636-642.

16. Yuen GS, Gunning FM, Woods E, Klimstra SA, Hoptman MJ, Alexopoulos GS. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. *J Affect Disord.* 2014;166:179-186.
17. Lavretsky H, Ballmaier M, Pham D, Toga A, Kumar A. Neuroanatomical characteristics of geriatric apathy and depression: a magnetic resonance imaging study. *Am J Geriatr Psychiatry.* 2007;15:386-394.
18. Brodaty H, Peters K, Boyce P, et al. Age and depression. *J Affect Disord.* Nov 1991;23:137-149.
19. Brodaty H, Luscombe G, Parker G, et al. Increased rate of psychosis and psychomotor change in depression with age. *Psychol Med.* 1997;27:1205-1213.
20. Shahpesandy H. Different manifestation of depressive disorder in the elderly. *Neuro Endocrinol Lett.* 2005;26:691-695.
21. Hegeman JM, Kok RM, van der Mast RC, Giltay EJ. Phenomenology of depression in older compared with younger adults: meta-analysis. *Br J Psychiatry.* 2012;200:275-281.
22. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci.* 1991;3:243-254.
23. Marin RS, Firinciogullari S, Biedrzycki RC. Group differences in the relationship between apathy and depression. *J Nerv Ment Dis.* 1994;182:235-239.
24. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord.* 1993;28:117-124.
25. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci.* 1998;10:314-319.
26. van Reekum R, Stuss DT, Ostrander L. Apathy: why care? *J Neuropsychiatry Clin Neurosci.* 2005;17:7-19.
27. Chase TN. Apathy in neuropsychiatric disease: diagnosis, pathophysiology, and treatment. *Neurotox Res.* 2011;19:266-278.
28. Mortby ME, Maercker A, Forstmeier S. Apathy: a separate syndrome from depression in dementia? A critical review. *Aging Clin Exp Res.* 2012;24:305-316.
29. Starkstein SE, Petracca G, Chmerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry.* 2001;158:872-877.
30. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry.* 2008;79(10):1088-1092.
31. Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry.* 2011;26:158-165.
32. American Psychiatric Association. Diagnostic and Statistical manual of mental disorders. 5th ed. United States: Washington, D.C.; 2013.
33. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res.* 1991;38:143-162.
34. Weiser M, Garibaldi G. Quantifying motivational deficits and apathy: a review of the literature. *Eur Neuropsychopharmacol.* 2015;25:1060-1081.

35. Strauss ME, Sperry SD. An informant-based assessment of apathy in Alzheimer disease. *Neuropsychiatry Neuropsychol Behav Neurol*. 2002;15:176-183.
36. Sockeel P, Dujardin K, Devos D, Deneve C, Destee A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006;77:579-584.
37. Robert PH, Clairet S, Benoit M, et al. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int J Geriatr Psychiatry*. 2002;17:1099-1105.
38. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4:134-139.
39. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. *Stroke*. 1993;24:1625-1630.
40. Okada K, Kobayashi S, Yamagata S, Takahashi K, Yamaguchi S. Poststroke apathy and regional cerebral blood flow. *Stroke*. 1997;28:2437-2441.
41. Chatterjee A, Anderson KE, Moskowitz CB, Hauser WA, Marder KS. A comparison of self-report and caregiver assessment of depression, apathy, and irritability in Huntington's disease. *J Neuropsychiatry Clin Neurosci*. 2005;17:378-383.
42. Tetsunaga T, Tetsunaga T, Tanaka M, Nishida K, Takei Y, Ozaki T. Effect of Tramadol/Acetaminophen on Motivation in Patients with Chronic Low Back Pain. *Pain Res Manag*. 2016 Epub doi:7458534.
43. Bertens AS, Moonen JE, de Waal MW, et al. Validity of the three apathy items of the Geriatric Depression Scale (GDS-3A) in measuring apathy in older persons. *Int J Geriatr Psychiatry*. 2016 Epub ahead; doi:10.1002/gps.4484.
44. Mehta M, Whyte E, Lenze E, et al. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *Int J Geriatr Psychiatry*. 2008;23:238-243.
45. Starkstein SE, Ingram L, Garau ML, Mizrahi R. On the overlap between apathy and depression in dementia. *J Neurol Neurosurg Psychiatry*. 2005;76:1070-1074.
46. Massimo L, Evans LK. Differentiating subtypes of apathy to improve person-centered care in frontotemporal degeneration. *J Gerontol Nurs*. 2014;40:58-65.
47. Yao H, Takashima Y, Mori T, et al. Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: the Sefuri brain MRI study. *Hypertens Res*. 2009;32:586-590.
48. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr*. 2010;22:819-829.
49. Onyike CU, Sheppard JM, Tschanz JT, et al. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry*. 2007;15:365-375.

50. Wongpakaran N, van Reekum R, Wongpakaran T, Clarke D. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Ann Gen Psychiatry*. 2007 Epub doi:10.1186/1744-859X-6-7.
51. Lampe IK, Heeren TJ. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *Int Psychogeriatr*. 2004;16:481-486.
52. Ligthart SA, Richard E, Fransen NL, et al. Association of vascular factors with apathy in community-dwelling elderly individuals. *Arch Gen Psychiatry*. 2012;69:636-642.
53. Lavretsky H, Lesser IM, Wohl M, Miller BL, Mehringer CM. Clinical and neuroradiologic features associated with chronicity in late-life depression. *Am J Geriatr Psychiatry*. 1999;7:309-316.
54. Eurelings LS, Richard E, Eikelenboom P, van Gool WA, Moll van Charante EP. Low-grade inflammation differentiates between symptoms of apathy and depression in community-dwelling older individuals. *Int Psychogeriatr*. 2015;27:639-647.
55. Bisoendial RJ, Boekholdt SM, Vergeer M, Stroes ES, Kastelein JJ. C-reactive protein is a mediator of cardiovascular disease. *Eur Heart J*. 2010;31:2087-2091.
56. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9:46-56.
57. Eurelings LS, Ligthart SA, van Dalen JW, Moll van Charante EP, van Gool WA, Richard E. Apathy is an independent risk factor for incident cardiovascular disease in the older individual: a population-based cohort study. *Int J Geriatr Psychiatry*. 2014;29:454-463.
58. Dujardin K, Sockeel P, Dellioux M, Destee A, Defebvre L. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Mov Disord*. 2009;24:2391-2397.
59. Starkstein SE, Brockman S, Bruce D, Petracca G. Anosognosia is a significant predictor of apathy in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 2010;22:378-383.
60. Derouesne C, Thibault S, Lagha-Pierucci S, Baudouin-Madec V, Ancrì D, Lacomblez L. Decreased awareness of cognitive deficits in patients with mild dementia of the Alzheimer type. *Int J Geriatr Psychiatry*. 1999;14:1019-1030.
61. Samus QM, Rosenblatt A, Steele C, et al. The association of neuropsychiatric symptoms and environment with quality of life in assisted living residents with dementia. *Gerontologist*. 2005;45 Spec No 1:19-26.
62. Bostrom F, Jonsson L, Minthon L, Londos E. Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2007;21:150-154.
63. Bhattacharya S, Vogel A, Hansen ML, Waldorff FB, Waldemar G. Generic and disease-specific measures of quality of life in patients with mild Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2010;30:327-333.
64. Yeager CA, Hyer L. Apathy in dementia: relations with depression, functional competence, and quality of life. *Psychol Rep*. Jun 2008;102:718-722.

65. Gerritsen DL, Jongenelis K, Steverink N, Ooms ME, Ribbe MW. Down and drowsy? Do apathetic nursing home residents experience low quality of life? *Aging Ment Health*. 2005;9:135-141.
66. Vinkers DJ, Stek ML, Gussekloo J, Van Der Mast RC, Westendorp RG. Does depression in old age increase only cardiovascular mortality? The Leiden 85-plus Study. *Int J Geriatr Psychiatry*. 2004;19:852-857.
67. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am J Psychiatry*. 2005;162:1588-1601.
68. Oguru M, Tachibana H, Toda K, Okuda B, Oka N. Apathy and depression in Parkinson disease. *J Geriatr Psychiatry Neurol*. 2010;23:35-41.
69. Comijs HC, Nieuwesteeg J, Kok R, et al. The two-year course of late-life depression; results from the Netherlands study of depression in older persons. *BMC Psychiatry*. 2015;15:20 doi: 10.1186/s12888-015-0401-5.
70. Drijgers RL, Aalten P, Winogrodzka A, Verhey FR, Leentjens AF. Pharmacological treatment of apathy in neurodegenerative diseases: a systematic review. *Dement Geriatr Cogn Disord*. 2009;28:13-22.
71. Thomas P, Clement JP, Hazif-Thomas C, Leger JM. Family, Alzheimer's disease and negative symptoms. *Int J Geriatr Psychiatry*. 2001;16:192-202.
72. Kaufer DI, Cummings JL, Christine D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc*. 1998;46:210-215.
73. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex*. 2006;16:916-928.
74. Radakovic R, Abrahams S. Developing a new apathy measurement scale: Dimensional Apathy Scale. *Psychiatry Res*. Nov 30 2014;219:658-663.



The background of the page is an abstract composition of numerous overlapping brushstrokes. The colors are primarily shades of teal, light blue, and dark blue, with some areas appearing more like a textured grey or brown. The strokes vary in length, thickness, and direction, creating a sense of movement and depth. Some strokes are straight and diagonal, while others are curved or horizontal. The overall effect is a complex, layered texture that resembles a close-up of a painted surface or a dense thicket of dry grass.

Appendix

Appendix

Apathie Schaal

	In het geheel niet aanwezig	Weinig aanwezig	Aanwezig	Sterk aanwezig
1. Heeft u belangstelling om dingen te leren?				
2. Heeft iets uw interesse?				
3. Bent u bezorgd om uw gezondheid?				
4. Steekt u veel energie in de dingen die u doet?				
5. Bent u altijd op zoek naar dingen die u kunt doen?				
6. Heeft u plannen en stelt u zichzelf doelen voor de toekomst?				
7. Bent u gemotiveerd?				
8. Heeft u voldoende energie voor uw dagelijkse bezigheden?				
9. Is het nodig dat een ander u zegt wat u op een dag moet doen?				
10. Maakt het u allemaal niet uit wat er gebeurt?				
11. Bent u niet meer betrokken bij veel dingen?				
12. Hebt u een aanzet nodig om ergens aan te beginnen?				
13. Voelt u zich niet opgewekt of verdrietig, maar iets daartussenin?				
14. Zou u zichzelf apathisch noemen?				

Starkstein et al. 1992

Scoring

Voor vragen 1-8:

3 = In het geheel niet aanwezig

2 = Weinig aanwezig

1 = Aanwezig

0 = Sterk aanwezig

Voor vragen 9-14:

0 = In het geheel niet aanwezig

1 = Weinig aanwezig

2 = Aanwezig

3 = Sterk aanwezig

Interpretatie totaalscore (0-42) Als afkapwaarde tussen lage en hoge scores voor apathie wordt 14 punten gehanteerd.



The background of the page is an abstract composition of numerous overlapping brushstrokes. The colors are primarily shades of blue, ranging from light, airy tones to deep, dark blues, with some white highlights. The strokes vary in thickness and direction, creating a sense of movement and texture. Some strokes are straight and diagonal, while others are curved or horizontal. The overall effect is a complex, layered visual field.

Nederlandse samenvatting

Nederlandse samenvatting

Achtergrond

Het in dit proefschrift beschreven onderzoek heeft als belangrijkste doel om verschillende aspecten van apathie, als een afzonderlijk klinisch relevant syndroom, bij ouderen met en zonder bijkomende depressie na te gaan. Hoewel het begrip 'apathie' al sinds eeuwen bestaat, is de betekenis ervan gedurende de tijd veranderd. Tegenwoordig betekent apathie als afzonderlijk klinisch syndroom een belangrijk verlies van motivatie dat interfereert met het dagelijks functioneren en dat tot uiting komt in verminderd doelgericht gedrag en doelgerichte cognitie en in een beperkte emotionele expressie. Apathie als afzonderlijk klinisch syndroom interfereert met de kwaliteit van leven en is geassocieerd met verschillende negatieve gezondheidsuitkomsten zoals hogere sterfte en minder baat hebben van rehabilitatie en behandeling van depressie.

Bij depressie op oudere leeftijd kan apathie zeer prominent aanwezig zijn; de kennis over apathie als een afzonderlijk klinisch relevant gedragssyndroom bij depressieve ouderen is echter schaars. In dit proefschrift wordt apathie bij zowel depressieve als niet-depressieve ouderen vanuit een breed perspectief onderzocht: de belangrijkste resultaten worden hieronder samengevat en besproken in de context van eerder onderzoek. Ook worden methodologische kwesties met betrekking tot de studie naar apathie bij ouderen behandeld, de klinische implicaties besproken en enkele aanbevelingen voor toekomstig onderzoek gedaan.

Resultaten

Subtypen van apathie

Volgens de diagnostische criteria wordt apathie als een stoornis van de motivatie gekenmerkt door symptomen in drie verschillende levensdomeinen: die van gedrag, cognitie en emotie. Onderscheiden symptoomprofielen van apathie zouden kunnen wijzen op verschillende subtypes, die gerelateerd zijn aan specifieke kenmerken en daarom verschillende behandelingen behoeven. Zulke subtypes van apathie kunnen niet onderscheiden worden door gebruik te maken van de (totaal)score van een meetinstrument. Om verschillende groepen personen ('Classes') te identificeren, hebben we daarom bij 122 ouderen met apathie, afkomstig uit een algemene bevolkingscohort van de PROMODE-studie, gebruik gemaakt van de data-gestuurde Latent Class Analysis (LCA) techniek (**Hoofdstuk 2**). Door gebruik te maken van LCA, konden we drie 'Classes' onderscheiden. Nader onderzoek van de kenmerken in

deze drie 'Classes' liet zien dat personen in 'Class' 2, in vergelijking met 'Class' 1 en 3, ernstiger apathisch en depressief waren, meer alcohol gebruikten en vaker alleen woonden. 'Class' 3 toonde, in vergelijking met de twee andere 'Classes', het laagst genoten opleidingsniveau, de laagste Mini-Mental State Examination (MMSE) score en de hoogste kwaliteit van leven. Er konden echter geen afzonderlijke subtypes van apathie worden aangetoond, aangezien alleen opleidingsniveau en ernst van apathie onafhankelijke voorspellers bleken te zijn voor 'Class'-lidmaatschap.

Apathie op oudere leeftijd

Hoewel apathie vaak samen met depressie voorkomt, is er toenemend bewijs dat apathie ook als een afzonderlijk klinisch relevant gedragsyndroom, onafhankelijk van depressie, kan optreden, met mogelijk een andere etiologie dan depressie. In **Hoofdstuk 3** beschrijven we de resultaten van de cross-sectionele studie onder de bij baseline depressieve en niet-depressieve ouderen in de NESDO-studie; we toonden aan dat klinisch relevante apathie bij 75% van de depressieve ouderen en 25% van de niet-depressieve ouderen aanwezig was. Depressieve en niet-depressieve ouderen met apathie verschilden van elkaar, aangezien de ernst van de depressieve symptomen bij depressieve ouderen geassocieerd was met de aanwezigheid van apathie, terwijl apathie bij niet-depressieve ouderen geassocieerd was met hogere C-reactive protein (CRP) spiegels. Bij zowel depressieve als niet-depressieve ouderen waren mannelijk geslacht en het hebben gehad van minder onderwijs onafhankelijk geassocieerd met de aanwezigheid van apathie.

Om de aanwezigheid en de impact van apathie bij depressieve ouderen verder te bestuderen, hebben we in **Hoofdstuk 4** de incidentie, het beloop en verschillende voorspellende factoren van apathie, na 2 jaar follow-up, onderzocht bij depressieve ouderen uit de NESDO-studie. De ernst van apathie, maar niet die van depressie, bij baseline voorspelde de ernst en persisteren van apathie evenals een slechter herstel van depressie bij follow-up. Daarnaast vonden we dat een slechter globaal cognitief functioneren bij baseline, maar niet de ernst van depressie, de 2-jaars incidentie van apathie voorspelde bij depressieve ouderen.

Hoewel depressie bij jongere volwassenen eveneens vaak gepaard gaat met apathie, heeft onderzoek laten zien dat de fenomenologie van depressie bij ouderen mogelijk verschilt van die van depressie bij jongere volwassenen. Dit zou vooral het geval kunnen zijn voor de aanwezigheid van (klinisch relevante) apathie, welke vaker voorkomt bij depressie op latere leeftijd. Daarom onderzochten we in **Hoofdstuk 5** de aanwezigheid en comorbiditeit van klinisch relevante apathie bij oudere in vergelijking met jongere depressieve personen. Het bleek dat van de 363 depressieve ouderen er 269 (75%) klinisch relevante apathie hadden, in vergelijking met 116 (54%) van de 217 jongere depressieve personen. Hoewel depressieve ouderen inderdaad vaker apathie vertoonden, bleken de geassocieerde risicofactoren in beide leeftijdsgroepen

grotendeels dezelfde te zijn, met uitzondering van roken dat specifiek geassocieerd was met apathie bij depressieve ouderen. In de gehele groep van zowel jongere als oudere depressieve personen was apathie onafhankelijk geassocieerd met hogere leeftijd, mannelijk geslacht en de aanwezigheid van een ernstiger depressie.

De last van apathie

Apathie is geassocieerd met een slechtere functionele uitkomst, chroniciteit en toegenomen algehele mortaliteit. Hoewel apathie een toegenomen belasting bij mantelzorgers geeft, is onbekend in welke mate apathie de patiënten zelf belast.

Hoofdstuk 6 laat de resultaten zien van ons onderzoek naar de ervaren kwaliteit van leven in relatie tot de aanwezigheid van klinisch relevante apathie, bij 1118 ouderen afkomstig uit de algemene bevolking in de PROMODE studie. Bij 122 (11%) van deze ouderen werd apathie gevonden. Bij 73 van deze ouderen met apathie, maar zonder depressieve symptomen en cognitieve beperkingen, was apathie geassocieerd met verminderde kwaliteit van leven wat betreft verschillende aspecten van het dagelijks leven. In tegenstelling tot niet-apathische ouderen ervaarden ouderen met zowel apathie als cognitieve beperkingen bovendien minder kwaliteit van leven op het gebied van de subjectieve gezondheid. Bij depressieve ouderen had apathie geen additioneel negatief effect op de reeds ervaren lage kwaliteit van leven.

Tot slot

In de algemene discussie van dit proefschrift wordt verder achtereenvolgens ingegaan op het concept apathie op latere leeftijd, op (het stellen van) de diagnose en het vaststellen van apathie met behulp van meetinstrumenten, en op apathie als een mogelijk heterogeen syndroom met verschillende subtypes, risicofactoren en behandeling. Daarna wordt het onderzoeksdesign tegen het licht gehouden en de algemene sterkten en zwakten van het onderzoek beschreven. Tenslotte worden mogelijke klinische implicaties geschetst en enkele suggesties voor toekomstig onderzoek gedaan.



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Curriculum Vitae

Curriculum Vitae

Isis Koolhoven werd geboren op 6 november 1968 in Tilburg. In 1987 behaalde zij het Gymnasium diploma aan het Stedelijk Gymnasium in 's-Hertogenbosch. In 1988 behaalde ze haar propedeuse psychologie aan de Katholieke Universiteit Brabant in Tilburg en startte haar studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Tussen 1990 en 1993 deed zij haar wetenschappelijke stage en aansluitend een student-assistentenschap bij de afdeling psychiatrie van het Academisch Ziekenhuis Rotterdam-Dijkzigt (heden: Erasmus Medisch Centrum) onder supervisie van Prof. dr. R.C. van der Mast, psychiater.

In 1995 behaalde zij haar artsdiploma en werkte een aantal maanden als wisselarts in het Ruwaard van Putten ziekenhuis in Spijkenisse. Van 1995 tot 1997 was zij werkzaam als anios op de afdeling neurologie van het Academisch Ziekenhuis Rotterdam-Dijkzigt (heden: Erasmus Medisch Centrum).

Vanaf 1997 werkte zij als anios bij De Grote Rivieren (heden: Yulius) en startte haar opleiding tot psychiater in 1999 welke zij afgerond heeft in 2004 (opleiders achtereenvolgend: dr. L. Wunderink en dr. G. Faber). Haar sociale psychiatrie stage heeft ze gedaan bij RIAGG Rijnmond Zuid (opleider: drs. A.A. de Groot). Als keuzestage werkte ze bij de ambulante ouderenpsychiatrie van De Grote Rivieren (heden: Yulius) en behaalde deeltijds haar ECT certificaat in het Erasmus Medisch Centrum (opleider: Prof. dr. W.W. van de Broek).

Van 2004 tot 2005 werkte zij als ouderenpsychiater op de ouderenkliniek De Gantel bij De Grote Rivieren (heden: Yulius). Hierna werkte zij tot 2007 als ouderenpsychiater bij het klinisch centrum ouderen van Parnassia in Den Haag waarbij zij tevens participeerde in het ECT team.

Sinds 2007 werkt zij als ouderenpsychiater bij Bavo Europaort (heden: Parnassia Bavo Groep), tot 2011 vooral ambulant en deeltijd, daarna als behandelinhoudelijk verantwoordelijke in de ouderenkliniek in Rotterdam. Eind 2009 is zij gestart met haar promotieonderzoek bij Roos van der Mast, hoogleraar ouderenpsychiatrie in het LUMC. Na het opzetten van de opleiding ouderenpsychiatrie voor het aandachtsgebied is zij sinds 2012 opleider voor het aandachtsgebied ouderenpsychiatrie. Vanaf 2015 is zij als leider van het specialisme Ouderen van de Parnassia Groep werkzaam en actief betrokken bij het consultatieteam Euthanasie binnen de Parnassia Bavo Groep.



The background of the page is an abstract composition of numerous overlapping brushstrokes. The colors are primarily shades of blue, ranging from a pale, almost white light blue to a deep, dark navy blue. The strokes vary in thickness and direction, creating a sense of movement and texture. Some strokes are straight and sharp, while others are more fluid and curved. The overall effect is a complex, layered visual field that suggests a sense of depth and artistic expression.

Publicaties

Publicaties

- **Koolhoven I**, Tjon-A-Tsien MRS, Van der Mast RC. Early diagnosis of delirium after cardiac surgery. *General Hospital Psychiatry* 1996; 18: 448-451
- Logmans A, Schoenmakers CH, Haensel SM, **Koolhoven I**, Trimbos JB, van Lent M, van Ingen HE. High tissue factor concentration in the omentum, a possible cause of its hemostatic properties. *Eur J Clin Invest* 1996; 26: 82-83
- **Groeneweg-Koolhoven**, MD, M.W.M de Waal, PhD, G.M. van der Weele, MD, PhD, J.Gussekkloo, MD PhD, R.C. van der Mast, MD PhD1. Quality of life in community dwelling older persons with apathy. *Am J Geriatr Psychiatry* 2014; 22: 186-194 Doi: 0.1016/j.jagp.2012.10.024
- **Isis Groeneweg-Koolhoven**, MD, Hannie C Comijs, PhD, Paul Naarding, MD PhD, Margot WM de Waal, PhD, Roos C van der Mast, MD PhD. Presence and correlates of apathy in non-demented depressed and non-depressed older persons. *Eur. J. Psychiat.* 2015; 29: 119-130
- **I. Groeneweg-Koolhoven**, L.J. Huitema, M.W.M. de Waal, M.L. Stek, R.C. van der Mast, D. Rhebergen. Latent Class Analysis of the Apathy Scale does not identify subtypes of apathy in a general population based older persons. *Int J Geriatr Psychiatry* 2016; 31: 1021-1028 DOI: 10.1002/gps.4413
- **I. Groeneweg-Koolhoven**, H.C. Comijs, P. Naarding, M.W.M. de Waal, R.C. van der Mast. Apathy in depressed older persons: course and predictors. The NESDO study. *J. Geriatr. Psychiatry Neurol.* 2016; 29: 178-186 DOI: 10.1177/0891988716632914
- **Isis Groeneweg-Koolhoven**, Merel Ploeg, Hannie C Comijs, Brenda WJH Penninx, Roos C. van der Mast, Robert Schoevers, Didi Rhebergen, Eric Exel. Apathy in Early and Late-life depression. *J Aff Dis* 217; 223: 76-81
- M Landman, SDM Theuns - Valks, HM van Wering, GA Tramper - Strandens, M van Ledden, E Rietveld, N van der Lelij, **I Groeneweg – Koolhoven**, JC Escher, M Groeneweg. Implementation of the 2012 ESPGHAN guideline of Coeliac Disease in children. Results of a retrospective study in the Netherlands. Submitted to *Eur J Pediatrics*.





Dankwoord

Dankwoord

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