Prevalence, symptoms and risk profiles of apathy at old age

Koolhoven, I.

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 antidepressants[8] and chronicity of depression[9] 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]

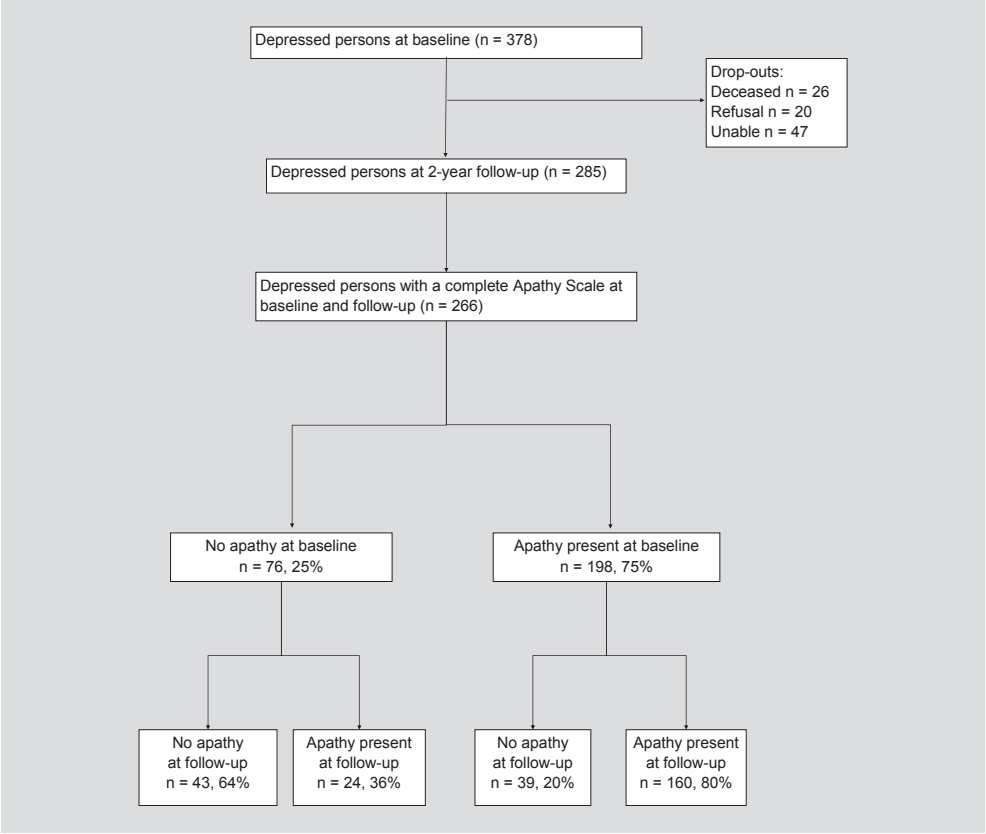

Figure 1. Flow chart research population (n=266)

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				
Total chronic disease	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
Number of medications used	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 + 0.057x age - 0.61 x gender + 0.749 x antihypertensive medication + 0.008 x syst. BP + 0.458 x smoking + 0.18 x cholesterol – 0.234 x HDL cholesterol + 0.857 x DM*;

[f] Geometric mean and 95% CI

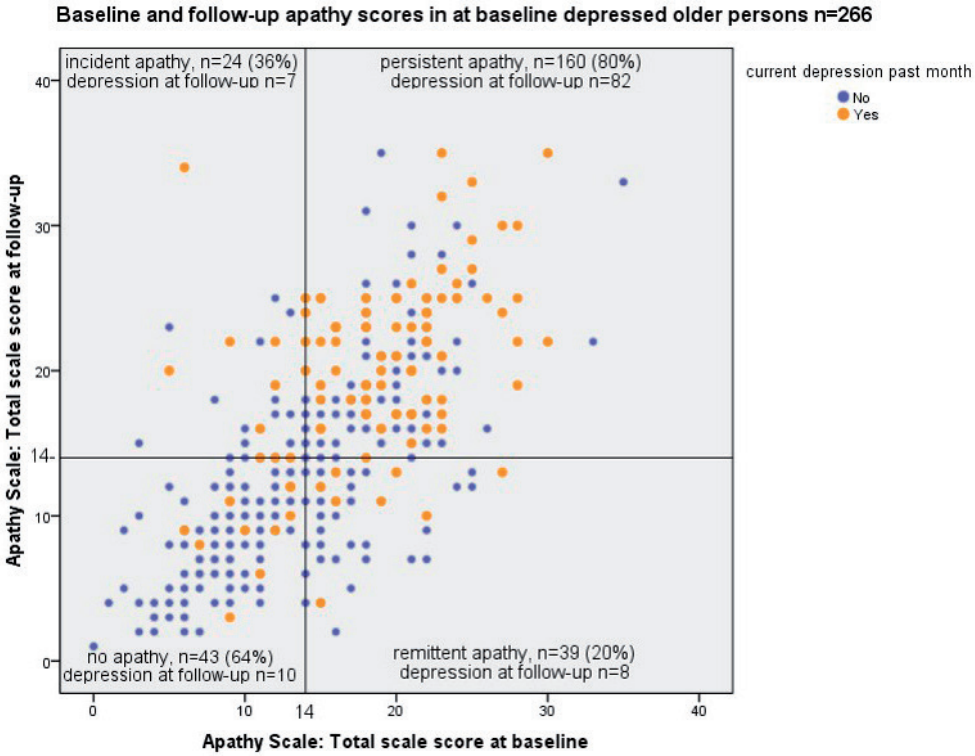

Figure 2. Incident (36%) and persistent apathy (80%), after 2 year follow-up, in older persons with a depressive disorder at baseline in and the relation with remission of the depressive disorder

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 $k = -8.65 + 0.057x\ age - 0.61\ x\ gender + 0.749\ x\ antihypertensive\ medication + 0.008\ x\ syst.\ BP + 0.458\ x\ smoking + 0.18\ x\ cholesterol - 0.234\ x\ HDL\ cholesterol + 0.857\ x\ DM$;

[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)

	Multivariate analyses			
	OR	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	0.3-27	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 + 0.057x age - 0.61 x gender + 0.749 x antihypertensive medication + 0.008 x syst. BP + 0.458 x smoking + 0.18 x cholesterol – 0.234 x HDL cholesterol + 0.857 x 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)

	Multivariate analyses			
	OR	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-iem 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-methyldopa, 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 Disease[25] 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 persons[41] 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 antidepressants[8] 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.

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