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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 socio-demographic, 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 aetiology for apathy in its own right.

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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 disease[2] 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 aetiologies possibly different from depression. Recent literature showed that among community-dwelling older persons free from depressive and apathy symptoms at baseline, 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 per-

sons, based on the literature, with cognitive impairment, vascular disease, frailty and immune activation.

Method

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).

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 = 0.90) and inter-rater (r = 0.81) 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 socio-demographic 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

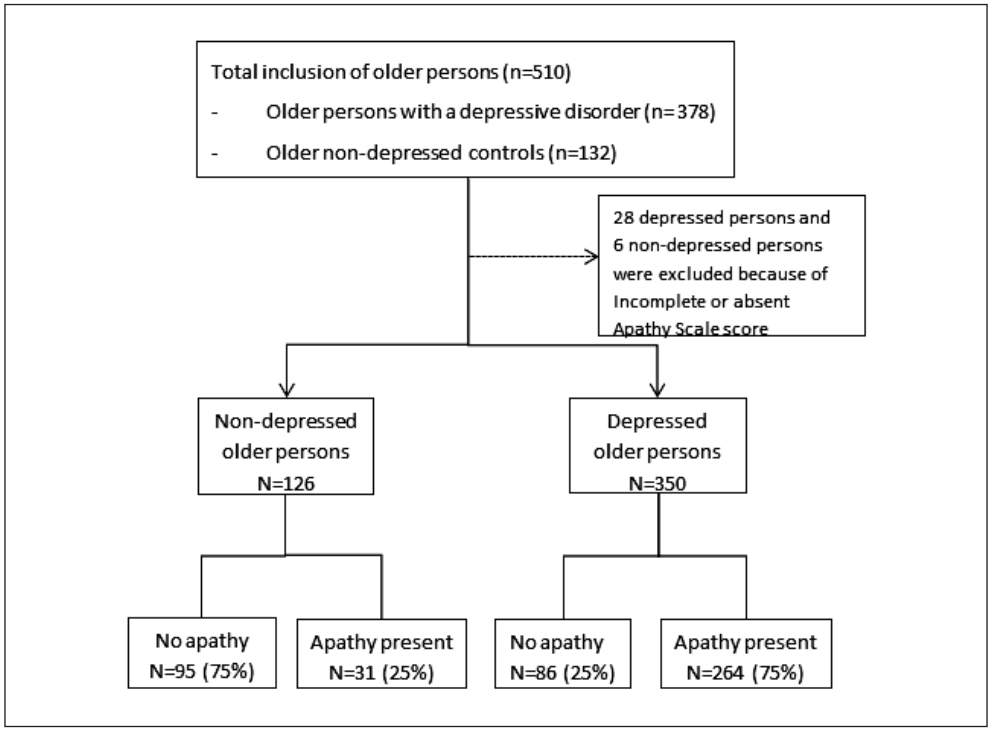

Figure 1. Flow chart included persons.

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 = 86) 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.

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 people may be due to the use of the self-administered method to asses 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 depres-

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†
Sociodemographic characteristics						
Age in years, mean (SD)	70	(8)	71	(7)	348 (0.70)	0.20
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						
*Presence of chronic disease**	26	(30)	101	(38)	1	0.20
Cardiovascular disease[#]	27	(31)	95	(36)	1	0.50
Diabetes Mellitus	8	(9)	34	(13)	1	0.50
Arthritis/rheuma	39	(45)	144	(55)	1	0.20
Chronic lung disease	11	(13)	42	(16)	1	0.60
*Presence of pain^*						
Intensity	40	(26-61)	50	(33-63)		0.09
Disability	25	(0-53)	32	(3-63)		0.10
Medication use	84	(98)	261	(99)	1	0.80
Psychotropic medication°	66	(77)	215	(81)	1	0.20
Benzodiazepines	27	(31)	109	(41)	1	0.30
Antidepressants	58	(67)	197	(75)	1	0.20
Antipsychotics	10	(12)	38	(14)	1	0.50
Analgesic medication[a]	24	(28)	90	(33)	1	0.40
Neuropsychiatric characteristics						
IDS score	22	(15-31)	31	(22-41)		< 0.005
AS score	10	(8-12)	19	(17-22)		< 0.005
MMSE score[$]	28	(27-29)	28	(27-29)		0.3
Biological characteristics						
Albumine (g/l)	42	(40-44)	42	(40-45)		0.60
IL6 (pg/ml)§	0.8	(0.6-1)	0.8	(0.7-1)	340 (0.01)	0.50
CRP (mg/l)§	1.7	(1.3-2.2)	2.1	(1.8-2.4)	336 (0.60)	0.30
Walking speed (sec.)§	6.4	(5.9-7)	7.1	(6.7-7.4)	344 (0.30)	0.03

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

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

*presence of chronic disease is defined by the median cut-off score of numbers of chronic diseases;

[#]included coronar, vascular and cerebral;

^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;

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

[a]Analgesic includes the use of peripheral working analgesic medication, NSAID's and analid;

[$]subjects with Mini Mental Status Examination < 19 were excluded;

†p-values by chi-square or Mann-Whitney where appropriate;

§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†
Sociodemographic characteristics						
Age in years, mean (SD)	69	(6)	73	(8)	42 (6.1)	0.030
Female gender	62	(65)	16	(52)	1	0.300
Education in years	12	(10-15)	11	(9-12)		0.001
Current partner	77	(81)	19	(61)	1	0.045
Clinical characteristics						
*Presence of Chronic disease present**	41	(43)	13	(42)	1	1
Cardiovascular disease#	17	(18)	13	(42)	1	0.010
Diabetes Mellitus	11	(12)	5	(16)	1	0.700
Arthritis/rheuma	44	(46)	16	(52)	1	0.800
Chronic lung disease	8	(8)	1	(3)	1	0.600
Pain^						
intensity	30	(0-43)	30	(10-53)		0.400
disability	0	(0-20)	0	(0-37)		0.900
Medication use	79	(83)	28	(90)	1	0.500
Psychotropic medication°	1	(1)	4	(13)	1	< 0.005
Benzodiazepines	1	(1)	2	(6)	1	0.300
Antidepressants	0	(0)	2	(6)	1	0.060
Antipsychotics	0	(0)	0	(0)	1	–
Analgesic medication	14	(15)	11	(36)	1	0.020
Neuropsychiatric characteristics						
IDS score	6	(4-9)	7	(5-12)		0.040
AS score	9	(6-11)	16	(14-17)		< 0.005
MMSE score$	29	(28-30)	28	(27-29)		0.040
Biological characteristics						
Albumin (g/l)	42	(40-45)	43	(41-46)		0.300
IL6 (pg/ml)§	0.7	(0.6-0.9)	1.1	(0.8-1.6)	121 (1.2)	0.049
CRP (mg/l)§	1.4	(1.1-1.7)	2.8	(1.96-3.9)	119 (0.1)	< 0.005
Walking speed (sec.)§	6	(5.6-6.4)	6.8	(6-7.6)	123 (0.4)	0.030

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

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

*presence of chronic disease is defined by the median cut-off score of numbers of chronic diseases;

#included coronar, vascular and cerebral;

^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;

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

[a]Analgesic includes the use of peripheral working analgesic medication, NSAID's and analid;

$subjects with Mini Mental Status Examination < 19 were excluded;

†p-values by chi-square or Mann-Whitney where appropriate;

§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	1.00	0.99-1.1	2.3	0.100
Female gender	0.40	0.2-0.7	8.8	< 0.005
Education in years	0.90	0.8-0.99	5.0	0.030
Pain intensity	0.99	0.98-1.0	0.7	0.400
IDS	1.10	1.0-1.1	22.2	< 0.005
Log_e walking speed (sec.)	1.30	0.5-2.95	0.3	0.600

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	0.500	0.500
Female gender	0.20	0.08-0.8	5.400	0.020
Education in years	0.80	0.7-0.9	6.900	0.008
Current partner	1.80	0.5-6.9	0.700	0.400
Cardiovascular disease present	1.30	0.4-4.6	0.200	0.700
Use of analgesic medication	1.80	0.5-6.8	0.800	0.400
IDS	1.10	0.96-1.2	1.600	0.200
MMSE	0.96	0.7-1.4	0.06	0.800
Log_e CRP (mg/l)	1.80	1.0-3.1	4.100	0.040
Log_e IL6 (pg/ml)	0.80	0.3-2.2	0.200	0.600
Log_e walking speed (sec.)	1.10	0.1-7.8	0.004	0.900

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.

sion, 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 ap-

athy[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 3,534 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 continues 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 people. 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 people 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 aetiology 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.

Disclosure

The authors declare that they have no conflicts of interest concerning this article. The authors have no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Author contributions

- *Study concept and design*: Comijs, Naarding, De Waal, Van der Mast
- *Acquisition of data*: Comijs, Naarding, De Waal, Van der Mast

– *Analysis and interpretation of data*: Groeneweg-Koolhoven, Comijs, Naarding, De Waal, Van der Mast
– *Drafting of the manuscript*: Groeneweg-Koolhoven, Comijs, Naarding, De Waal, Van der Mast
– *Critical revision of the manuscript for important intellectual content*: Groeneweg-Koolhoven, Comijs, Naarding, De Waal, Van der Mast
– *Final approval of the version to be published*: Groeneweg-Koolhoven, Comijs, Naarding, De Waal, Van der Mast
– *Guarantors*: Van der Mast

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