Apathy symptoms, physical and cognitive function, health-related quality of life, and mortality in older patients with CKD: a longitudinal observational study

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Apathy Symptoms, Physical and Cognitive Function, Health-Related Quality of Life, and Mortality in Older Patients With CKD: A Longitudinal Observational Study

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Rationale & Objective: Apathy reflects diminished motivation, goal-directed behavior, and emotions, as well as less engagement in social interactions. Apathy overlaps with depression and is associated with cognitive decline. In the older individuals with chronic kidney disease (CKD), both depression and cognitive impairments are common, but apathy symptoms have been underreported. We investigated the occurrence of apathy symptoms and their associations with physical and cognitive functioning, health-related quality of life (HRQoL), and mortality in older patients with CKD.

Study Design: Prospective observational cohort study.

Setting & Participants: 180 outpatients aged ≥65 years with estimated glomerular filtration rate ≤ 20 mL/min/1.73 m^2 from 5 Dutch nephrology centers.

Exposure: Apathy symptoms at baseline were considered present when a Geriatric Depression Scale's 3-item apathy subscale score was ≥2 points.

Outcome: Physical and cognitive functioning, HRQoL (assessed in annual geriatric assessments), and 4-year mortality.

Analytical Approach: Linear regression for cross-sectional associations, linear regression models for longitudinal associations, and Cox regression models for mortality over 4 years of observation.

Results: Apathy symptoms were present in 64 patients (36%; 67% men; median age 75.5 years), of whom 32 (50%) had no depressive symptoms. At baseline, the presence of apathy symptoms was associated with significantly more frailty, more functional dependence, less physical capacity, lower visuoconstructive performance, worse delayed recall, and lower HRQoL scores. The presence of apathy symptoms at baseline was also associated with a higher mortality risk (hazard ratio, 2.3 [95% CI, 1.3-4.2], $P = 0.005$ adjusted for age, sex, and high education level), but not with changes in physical and cognitive functioning or HRQoL during the follow-up period.

Limitations: Risk of selection bias and residual confounding.

Conclusions: Apathy symptoms were highly prevalent and associated with concurrent lower physical and cognitive status, lower HRQoL, and increased mortality. These findings highlight apathy as a potentially important clinical phenotype in older CKD patients.

Visual Abstract online

Complete author and article information provided before references.

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Apathy has been defined as a loss of motivation, reduced goal-directed behavior, diminished emotions, and less engagement in social interaction.[1] It can be a symptom of depression or cognitive impairment[2-5] but can also be observed as a syndrome in its own right.[6] Primarily in older populations, symptoms of apathy have been associated with subclinical cerebral small vessel disease.[7] Although depression and cognitive impairments, as well as vascular problems, are common in the older population with chronic kidney disease (CKD),[8-13] apathy symptoms have been underreported,[14-16] and the prevalence of apathy symptoms in CKD is unknown.

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In community-dwelling older persons, apathy has been associated with poor outcomes, including functional disability,[17] reduced (non)pharmacological therapeutic response,[18] lower quality of life,[19] high caregiver distress and burden,[20,21] and a higher risk of myocardial infarction, stroke, and all-cause mortality.[22,23] The risk of incident dementia[2-4,24] and mild cognitive impairment[5] was increased 2-fold among older persons with apathy symptoms. The older CKD population is growing and comprises an increasing proportion of frail and multimorbid patients.[25] It is unexplored whether apathy symptoms are associated with poor outcomes in older patients with CKD.

We investigated the occurrence of apathy symptoms in an older advanced CKD population (stages G4 to G5) and explored associations of the presence of apathy symptoms with physical and cognitive functioning, health-related quality of life (HRQoL), and mortality over time.

Methods

Study Design and Participants

Cognitive Decline in Older Patients with End-stage Kidney Disease (COPE) is a prospective, multicenter,

PLAIN-LANGUAGE SUMMARY

We observed that older kidney patients often present apathy symptoms, such as less motivation, fewer goal-directed behaviors, fewer emotions, and less social engagement. Prior research has not extensively described apathy in kidney disease. We investigated the link between apathy symptoms and poor outcomes. We measured physical functioning, cognitive functioning, and quality of life. We learned that one-third of our older kidney patients showed symptoms of apathy, only half of whom had symptoms of depression. Patients with apathy symptoms showed lower quality of life and lower physical and cognitive performance. They also had a higher risk of death. These findings highlight the need for awareness of apathy symptoms in older kidney patients.

observational cohort study in the Netherlands.[26] The participants were included from 5 hospitals between April 2014 and December 2019. They were eligible for study inclusion if they were ≥65 years old, had an estimated glomerular filtration rate (eGFR) below 20 mL/min/1.73 m^2, and attended the nephrology outpatient clinic. If patients had an acute event causing a drop of eGFR ≤ 20 mL/min/1.73 m^2, they were only included when the eGFR 3 months before acute kidney injury was ≤30 mL/min/1.73 m^2. In addition, the patients initiated (or had to initiate) counseling for support in decision-making about whether to start or forego kidney replacement therapy. Patients were excluded if they were illiterate, did not speak Dutch, or were unable to provide informed consent.

After giving informed consent, the patients underwent a geriatric assessment during routine outpatient care. The assessment included neuropsychological testing and measures of physical functioning and symptoms of depression, and it has been described in more detail elsewhere.[26,27] This assessment was repeated every year for 4 years, was conducted by trained geriatric or dialysis nurses, and included a consultation with a geriatrician. The study size was predefined.[26]

The research was conducted according to the principles of the Declaration of Helsinki and the Dutch Medical Research Involving Human Subjects Act (WMO) and approved by the Medical Ethics Committee Leiden (reference NL46389.058.13) and the participating centers accordingly. All participants provided written informed consent.

Measurements

Patient Characteristics

Demographic measures were assessed at baseline and included age, sex, living status, ethnic group, marital status/living situation, and level of education. Clinical parameters that were collected at baseline included body mass index and eGFR. The eGFR was assessed using the most common method in the different hospitals, either using the Modification of Diet in Renal Disease (MDRD) or the 2009 CKD-EPI Creatinine equation. In addition, we assessed alcohol use, current smoking status, history of diabetes mellitus, and history of vascular disease. History of vascular disease was defined as a past myocardial infarction and/or stroke and/or peripheral vascular disease. Primary kidney disease was assessed by the treating nephrologist according to the old European Renal Association coding system[28] and categorized into 2 groups: nonvascular and vascular etiology (ie, codes covering "renal vascular disease" and "diabetes mellitus"). Medication use was registered at baseline and summarized in groups, including glucose-lowering medication, antihypertensive drugs, diuretics, cholesterol-lowering drugs, vitamin D supplements, and psychiatric and sleeping medications. Polypharmacy was defined as chronic use of ≥5 drugs.

Symptoms of Apathy and Symptoms of Depression

Symptoms of apathy were assessed with the 3-item subscale (GDS-3A) of the 15-item Geriatric Depression questionnaire (GDS-15).[24,29-31] We defined apathy symptoms as a score of ≥2 on the 3 apathy items: (1) "Have you dropped many of your activities and interests?"; (2) "Do you prefer to stay at home, rather than go out and doing new things?"; (3) "Do you feel full of energy?" (reverse-coded). GDS-3A scores ≥2 have been shown to be indicative of apathy in older adults as detected with the Apathy Scale with a sensitivity of 29%-69% and a specificity of 85%-93%.[30-32] We applied this commonly used[22,32] cut-off of ≥2 to dichotomize the presence of apathy symptoms. Although research into the scale properties of the GDS-3A is limited, the GDS-3A was validated for use in research on apathy in older populations.[31] The presence of depressive symptoms was operationalized as a score ≥2 on the 12 remaining items of the GDS-15 (ie, GDS-12D). Previous studies informed these cutoffs.[22,29-31] Isolated apathy symptoms were defined as the presence of apathy symptoms and lack of depressive symptoms (GDS-3A ≥2 and GDS-12D ≤1). Patients with missing GDS items that potentially affect these cutoffs would be excluded from the analyses.

Physical and Cognitive Functioning, HRQoL, and Mortality

The annual geriatric assessment included measures of frailty, functional dependency, physical capacity to assess physical functioning, global cognition, visuoconstructive abilities, memory, executive function, and psychomotor speed for cognitive functioning. Self-reported HRQoL was assessed using the RAND 36-Item Health Survey physical health summary score and mental health summary score.[33] Table 1 provides a detailed description of the used instruments, their score ranges, and their interpretation. Date

Table 1. Instruments From Annual Geriatric Assessment Assessing Physical and Cognitive Functioning and HRQoL

Subdomain	Instrument	Explanation and Score Range
Domain: Physical Functioning		
Frailty	Fried Frailty Index (FFI)	• Assesses the frailty phenotype including weight loss, self-reported exhaustion, decreased activity, weakness, and slow mobility. • Higher scores (range 0-5) indicate more frailty.
Dependency	Groningen Activity Restriction Scale (GARS)	• 18 Items about activity of daily living such as bathing and dressing, ability to cook, clean, etc; scored from 1 (without any trouble) to 4 (only with help from others). • Total score ranged from 18-72 with higher scores indicating increased dependence.
Physical capacity	Handgrip strength	• Muscle weakness is measured with a Jaymar Handheld Dynamometer. • Average of 3 measurements was used. More strength (kg) indicates more physical capacity.
	Gait speed test	• Gait speed is measured using a timed 6-meter walking test. • Faster completion indicates more physical capacity.
Domain: Cognitive Functioning		
Global cognition	Mini-Mental State Examination (MMSE)	• Measures cognitive impairment, including functions of registration, attention and calculation, recall language, ability to follow simple commands and orientation. • Scores range from 0 to 30, with higher scores indicating better cognitive performance.
Visuo-constructive abilities	Clock drawing	• Assesses visuospatial and praxis abilities and may determine both attention and executive dysfunctions. • Score ranged between 0-14 based on accuracy, with higher scores representing better performance.
Memory	15-item Word Verbal Learning Test (15-WVLT)	• Evaluates short-term auditory-verbal memory. Five presentations of a 15-word list are given, each followed by an attempted recall. • *Immediate recall* score was calculated as the mean number of correct words repeated over 5 trials, ranging from 0 to 15. Higher scores indicate higher auditory memory function. • *Delayed recall* was measured after a 20 minutes delay, using the same 15-word list without a representation. • The number of correctly recalled words was scored (0-15 range).
	Visual Association Test (VAT)	• Evaluates visual long-term memory reproduction with the use of a brief learning task based on imagery mnemonics. • Score ranged from 0 to 12 with higher scores indicate better function.
Executive function	Trail Making Test B-A (TMTΔ)	• Assesses visual attention and task switching and provides information about visual search speed, scanning, speed of processing, and mental flexibility as well as executive functioning. • Trail Making Test B, corrected for the Trail Making Test A score (ie, TMTΔ). • Less time spent indicating better executive function.
	Stroop Color Word Test III-II (SCWT)	• Measures selective attention. It comprises 3 parts, each containing 100 elements: color names, colored patches, and color names printed in incongruously colored ink. • The SCWT-III (interference card) was corrected for the score on SCWT-II (color naming card) to discriminate between processing speed and cognitive inhibition as an explanation of the test result. • Less time spent indicates better executive function.
Psychomotor speed	Trail Making Test A (TMT-A)	See above.
	Stroop Color Word Test II (SCWT-II)	See above.
	Letter Digit Substitution Test (LDST)	• A speed-dependent task that requires a participant to match symbols (letters) with their corresponding digit. The LDST measures complex neuropsychological processes including sustained attention, psychomotor speed, and speed of information processing.

(Continued)

Table 1 (Cont'd). Instruments From Annual Geriatric Assessment Assessing Physical and Cognitive Functioning and HRQoL

Subdomain	Instrument	Explanation and Score Range
		• Higher scores of correct substitutions at 60 seconds indicate better functioning.
Domain: Health-related Quality of Life		
Physical and mental health summary score	RAND 36-Item Health Survey	• Self-reported health-related quality of life. Both the physical and mental summary scores range from 0-100, with higher scores indicating better functioning. • These scores are a weighted average normalized to a mean score of 50 ± 10 SD, using method of Ware et al.[33]

Further information on the used geriatric assessment, including references to the used instruments, was described by Berkhout et al.[26]

of death was derived from the electronic patient records within 4 years of follow-up observation.

Statistical Analysis

Baseline characteristics are presented for the total sample and stratified for the presence of apathy symptoms (yes/no): in frequencies with proportions for nominal and categorical data, mean with standard deviation for continuous normally distributed data, and median with interquartile range (IQR) for skewed data. In addition, we described baseline characteristics for patients with isolated apathy symptoms and those with both symptoms of apathy and depression. Differences in percentages between groups were tested using χ^2 tests.

We investigated the associations of the presence of apathy symptoms with physical and cognitive outcomes at baseline (cross-sectional) and over time (longitudinal). Cross-sectional associations between the presence of apathy symptoms and physical functioning (frailty, Groningen Activity Restriction Scale [GARS] score, handgrip strength, and walking speed), and cognitive functioning (Mini-Mental State Examination [MMSE] score, clock drawing, 15-WVLT, 15-item Word Verbal Learning Test [15-WVLT] immediate and delayed recall score, Visual Association Test [VAT] score, Trail Making Test [TMT] Δ, Stroop Color Word Test [SCWT] III-II, Letter Digit Substitution Test [LDST], TMT-A, and SCWT II) at baseline were investigated comparing mean scores using linear regression. Longitudinal analyses of up to 5 repeated measurements were conducted to investigate whether the presence of apathy symptoms at baseline was associated with a change in physical status and cognitive function over 4 years of follow-up.

Linear regression models with correlated errors were used, which allow a varying number of follow-up measurements across individuals, including a single measurement. Comparable to a mixed model using random effects, generalized least squared regression models describe how the mean outcome changes in time and whether this change depends on certain confounders while taking the within-subject correlation into account. We proceeded with this model because data were collected at approximately the same time points for all participants and follow-up is not extensively long.[34] The presence of apathy at baseline was included in the model as a fixed independent variable, the follow-up time point as a continuous fixed variable, and the previously mentioned physical and cognitive outcomes as continuous dependent variables. The interaction between apathy and follow-up time point was included, indicating the annual additional change in outcomes for patients with apathy symptoms compared with patients without apathy symptoms. Additionally, the analysis was adjusted for age, sex, and high educational level as potential confounders.

To examine the association between the presence of apathy symptoms and mortality, we plotted Kaplan-Meier survival curves for patients with and without apathy symptoms and computed Cox proportional hazards regression models to assess mortality risks. The proportional hazard assumption was checked with a time-dependent Cox model for each of the independent variables. The analysis was performed crude and adjusted for potential confounders, including age, sex, high educational level, history of diabetes mellitus, and history of vascular disease.

All analyses were conducted in SPSS Statistics version 25 (IBM Corp). $P < 0.05$ was considered statistically significant. We did not correct for multiple testing because of the exploratory character of our study. We adhered to the guidelines for reporting observational studies (ie, the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] Statement).[35]

Sensitivity Analysis

Sensitivity analyses were performed to distinguish associations of symptoms of apathy from depressive symptoms. We repeated all cross-sectional, longitudinal, and survival analyses for patients with isolated apathy symptoms (ie, excluding those with apathy and depressive symptoms) versus patients without apathy symptoms.

Results

Table 2 presents the baseline characteristics of the 180 included patients. The median age was 76 years old (IQR, 71-81), and most participants were male (67%) and lived together with a partner (62%). Mean eGFR at study enrollment was 16.2 mL/min/1.73 m^2 (± 4.6 SD). The

Table 2. Baseline Characteristics of the Study Population

	Total Sample n = 180	Apathy Symptoms		*P* Value
		Absent n = 116 (64%)	Present n = 64 (36%)	
Age, y	75.5 [71.0-81.0]	75.2 [70.7-81.0]	77.0 [71.7-81.0]	0.5
Male gender	120 (66.7%)	79 (68.1%)	41 (64.1%)	0.6
White	159 (89.3%)	103 (89.6%)	56 (88.9%)	0.9
Married/living together	107 (61.5%)	73 (64.6%)	34 (55.7%)	0.3
Higher education level	62 (34.6%)	40 (34.5%)	22 (34.9%)	0.9
Current smoking	23 (13.1%)	14 (12.4%)	9 (14.5%)	0.7
Alcohol consumption	90 (51.4%)	65 (57.5%)	25 (40.3%)	0.03
Body mass index, kg/m^2	27.7 ± 4.6	27.3 ± 3.9	28.5 ± 5.5	0.1
Disease Specific				
eGFR at study enrollment, mL/min/1.73 m^2	16.5 ± 4.6	16.3 ± 4.6	16.7 ± 4.7	0.6
Δ eGFR[a]	−9.5 ± 8.6	−9.0 ± 7.7	−10.4 ± 9.9	0.4
Vascular primary kidney disease[b]	100 (61.3%)	58 (55.2%)	42 (72.4%)	0.03
History of diabetes mellitus	74 (41.1%)	43 (37.1%)	31 (48.4%)	0.1
History of vascular disease	89 (49.7%)	52 (45.2%)	37 (57.8%)	0.1
Medication Use				
Polypharmacy (the use of ≥5 medications)	161 (89.4%)	104 (90.4%)	57 (90.5%)	0.9
Glucose-lowering medication	64 (35.6%)	37 (31.9%)	27 (42.2%)	0.2
Antihypertensive medication	162 (90.0%)	108 (93.1%)	54 (84.4%)	0.06
Diuretics	107 (59.8%)	63 (54.8%)	44 (68.8%)	0.07
Cholesterol-lowering drugs	127 (70.6%)	80 (69.0%)	47 (73.4%)	0.5
Vitamin D supplement	151 (83.9%)	94 (81.0%)	57 (89.1%)	0.2
Psychiatric medication[c]	13 (7.2%)	9 (7.8%)	4 (6.3%)	0.7
Sleep medication	18 (10.1%)	8 (6.9%)	10 (15.6%)	0.07
Depressive Symptoms				
Present (GDS-12D score ≥2)	59 (32.8%)	27 (23.3%)	32 (50.0%)	<0.001

Data are presented as frequencies with proportions for nominal and categorical data, mean ± SD for continuous normally distributed data, and median [IQR] for skewed data. Missing data for apathy symptoms absent versus present: married/living together, n = 3 (2.6%) vs n = 3 (4.7%); White, n = 1 (0.9%) vs n = 1 (1.6%); education level, n = 0 vs n = 1 (0.6%); current smoking, n = 3 (2.6%) vs n = 2 (3.1%); alcohol consumption, n = 3 (2.6%) vs n = 2 (3.1%); body mass index, n = 1 (0.9%) vs n = 1 (1.6%); eGFR, n = 3 (2.6%) vs n = 4 (6.3%); Δ eGFR, n = 20 (17.2%) vs n = 11 (17.1%); primary kidney disease, n = 11 (9.5%) vs n = 6 (9.4%), of which n = 9 unknown etiology and n = 8 missing data; history of vascular disease, n = 1 (0.9%) vs n = 0; polypharmacy, n = 1 (0.9%) vs n = 1 (1.6%); diuretics, n = 1 (0.9%) vs n = 0; and sleep medication, n = 2 (1.7%) vs n = 0.

Abbreviations: eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; GDS-12D, Geriatric depression scale 12-item subscale for depressive symptoms.

[a]Δ eGFR indicates the decline in eGFR in the 3 years before study enrollment.

[b]Vascular primary kidney disease was defined by codes 70, 71, 72, 73, 80, and 81 of the old ERA coding system.[28]

[c]Psychiatric medication included anxiolytics, benzodiazepines, and antidepressants.

majority (61%) had a vascular cause of kidney disease, and half the participants had a history of vascular disease (50%). Polypharmacy and use of antihypertensive drugs were frequent (89% and 90%, respectively). Depressive symptoms were present in 23% (n = 58). Missing items for the GDS-12D subscale (n = 4) did not affect the used cutoff score for depressive symptoms.

GDS-3A scores were available for all patients. Apathy symptoms (GDS-3A ≥ 2) were present in 36% (n = 64) of the population. Patients with apathy symptoms more often had a vascular cause of kidney disease (n = 42, 72%) compared with the patients without apathy symptoms (n = 58, 55%, P = 0.031). Age, sex, education level, the change in kidney function in the 3 years before the study, and medication use did not differ between the groups. Depressive symptoms were significantly more prevalent in patients with apathy symptoms (50%, n = 32) compared with the patients without apathy symptoms (23%, n = 27, P ≤ 0.001). There was no difference in baseline characteristics between the patients with isolated apathy symptoms and those with combined apathy and depressive symptoms (Table S1).

Cross-sectional Associations of Apathy With Physical and Cognitive Functioning, and HRQoL

Table 3 shows the association of the presence of apathy symptoms with physical and cognitive performance and HRQoL at baseline. Patients with apathy symptoms had higher frailty scores (mean Fried Frailty Index 2.5 vs 1.2; P < 0.001), more functional dependency (mean GARS score 31.4 vs 26.2; P < 0.001), and lower physical capacity (mean handgrip strength 23.2 kg vs 26.7 kg; P = 0.021; mean walking speed 0.9 vs 1.1 m/s; P < 0.001) compared with the patients without apathy symptoms. These differences remained

Table 3. Baseline Associations of the Presence of Apathy Symptoms With Measures of Physical and Cognitive Functioning in 180 Patients With CKD Aged 65 Years and Older

	Apathy Symptoms		Difference	
	Absent n = 116	Present n = 64	Unadjusted	Adjusted[a]
Physical Functioning				
Frailty, FFI, range 0-5[b]	1.21 ± 1.21	2.48 ± 1.39	1.27 (0.88 to 1.66)[c]	1.22 (0.84 to 1.59)[c]
Dependency, GARS score, range 18-72[b]	26.22 ± 9.83	31.38 ± 9.42	5.15 (2.18 to 8.13)[c]	5.05 (2.21 to 7.87)[c]
Physical capacity				
Handgrip strength, kg	26.72 ± 9.04	23.20 ± 10.59	−3.53 (−6.51 to −0.53)[c]	−2.82 (−5.12 to −0.52)[c]
Walking speed, m/s	1.11 ± 0.33	0.87 ± 0.29	−0.24 (−0.34 to −0.13)[c]	−0.23 (−0.32 to −0.13)[c]
Cognitive Functioning				
Global cognition, MMSE score, range 0-30	28.03 ± 1.88	27.70 ± 2.37	−0.32 (−0.96 to 0.31)	−0.33 (−0.95 to 0.30)
Visuoconstruction, clock drawing, range 0-14	11.92 ± 1.79	11.17 ± 2.47	−0.75 (−1.45 to −0.04)[c]	−0.79 (−1.42 to −0.15)[c]
Memory				
Immediate recall, 15-WVLT, range 0-15	6.35 ± 1.95	5.81 ± 2.09	−0.54 (−1.15 to 0.08)	−0.55 (−1.14 to 0.03)
Delayed recall, 15-WVLT, range 0-15	6.11 ± 3.03	5.21 ± 3.11	−0.90 (−1.86 to 0.06)	−0.96 (−1.88 to −0.05)[c]
VAT, range 0-12	11.39 ± 1.45	10.98 ± 2.04	−0.40 (−0.93 to 0.12)	−0.42 (−0.92 to 0.08)
Executive function				
TMT B-A, s[b]	105.41 ± 61.96	119.58 ± 57.24	14.17 (−4.84 to 33.18)	14.08 (−4.29 to 32.45)
SCWT III-II, s[b]	85.60 ± 64.10	86.60 ± 48.65	0.76 (−17.74 to 19.27)	1.11 (−15.97 to 18.20)
Psychomotor speed				
LDLT, correct/min	22.07 ± 7.22	20.10 ± 6.35	−1.97 (−4.11 to 0.17)	−2.00 (−4.06 to 0.07)
TMT A, s[b]	67.52 ± 42.09	74.51 ± 41.99	6.99 (−6.00 to 19.98)	7.01 (−5.66 to 19.69)
SCWT II, s[b]	81.42 ± 29.70	87.08 ± 24.90	5.66 (−3.00 to 14.33)	5.95 (−2.66 to 14.56)
Health-related Quality of Life				
RAND-36 physical summary score	43.35 ± 11.25	33.83 ± 8.77	−9.52 (−12.62 to −6.42)[c]	−9.47 (−12.67 to −6.28)[c]
RAND-36 mental summary score	48.76 ± 8.71	41.66 ± 11.50	−7.09 (−10.50 to −3.69)[c]	−6.99 (−10.03 to −3.96)[c]

Figures are presented as mean ± SD for apathy symptoms and mean (95% CI) for difference. Missing data for apathy symptoms absent versus present: FFI, n = 0 vs n = 1 (0.6%); handgrip strength, n = 2 (1.7%) vs n = 2 (3.1%); walking speed, n = 7 (6.0%) vs n = 7 (10.0%); clock, n = 2 (1.7%) vs n = 1 (0.6%); WVLT delayed, n = 2 (1.7%) vs n = 3 (4.7%); VAT, n = 0 vs n = 2 (3.1%); TMT B-A n = 2 (1.7%) vs n = 4 (6.3%); SCWT III-II, n = 6 (5.2%) vs n = 2 (3.1%); LDLT, n = 0 vs n = 1 (1.6%); TMT A, n = 0 vs n = 1 (1.7%); SCWT II, n = 3 (2.6%) vs n = 0; RAND-36, n = 7 (6.0%) vs n = 5 (7.8%). Abbreviations: FFI, Fried Frailty Index; GARS, Groningen Activity Restriction Scale; LDST, Letter Digit Substitution Test; MMSE, Mini-Mental State Examination; SCWT, Stroop Color Word Test; TMT, Trail Making Test; VAT, Visual Association Test; 15-WVLT, 15-item Word Verbal Learning Test.
[a]Adjusted for age, sex, and high education level.
[b]Higher scores mean less performance.
[c]Statistically significant values.

statistically significant after adjustment for age, sex, and education level. Presence of apathy symptoms was associated with lower visuoconstructive performance (mean clock drawing score 11.2 vs 11.9; P = 0.037). Delayed memory function was significantly worse for patients with apathy symptoms only when adjusted for age, sex, and education level (mean difference in 15-WVLT delayed recall score −0.96 [95% CI, −1.9 to −0.1], P = 0.039). No statistically significant associations were found for the presence of apathy symptoms with global cognition (MMSE), visual memory (VAT), or psychomotor speed. HRQoL scores were lower for patients with apathy symptoms compared with those without, both in the physical and mental domain (−9.5 [95% CI, −12.6 to −6.4] and −7.1 [95% CI, −10.0 to −4.0], respectively).

Longitudinal Associations of Apathy With Physical and Cognitive Decline, and HRQoL

The median follow-up period was 30.7 months (IQR, 13.3-48.0), and complete 4-year follow-up was reached by n = 22 (12%) patients. Table 4 shows that on almost all physical and cognitive tests, mean annual change was comparable for patients with apathy symptoms to those without. Apart from the mean progression of the TMTΔ score (executive functioning) that indicated more decline in patients with apathy symptoms (ie, yearly mean 13.29 seconds less compared with those without apathy symptoms ([95% CI, 2.30-24.28], P = 0.018). Adjustment for age, sex and education level resulted in similar estimates of the difference in annual progression (13.94 [95% CI, 3.76-24.12], P = 0.008). The mean annual change in physical and mental HRQoL summary scores did not differ between the groups.

Table 4. Annual Change in Physical and Cognitive Functioning During Follow-up for Older CKD Patients With and Without Apathy Symptoms

Annual Change	Apathy Symptoms at Baseline		Difference in Annual Decline (Presence of Apathy at Baseline * Time)	
	Absent n = 116	Present n = 64	Unadjusted Model	Adjusted Model[a]
Physical Functioning[b]				
Frailty, FFI[c]	−0.00 ± 0.06	−0.03 ± 0.10	−0.03 (−0.26 to 0.21)	−0.01 (−0.24 to 0.22)
Dependency, GARS score[c]	1.07 ± 0.34	1.88 ± 0.52	0.81 (−0.42 to 2.04)	0.80 (−0.42 to 2.03)
Physical capacity				
Handgrip strength, in kg	−0.25 ± 0.31	−1.10 ± 0.46	−0.85 (−1.95 to 0.25)	−0.90 (−1.94 to 0.13)
Walking speed, in m/s	−0.01 ± 0.01	−0.02 ± 0.02	−0.02 (−0.07 to 0.03)	−0.02 (−0.07 to 0.03)
Cognitive Functioning[b]				
Global cognition, MMSE score	−0.01 ± 0.10	−0.14 ± 0.15	−0.12 (−0.48 to 0.24)	−0.13 (−0.49 to 0.23)
Visuoconstruction, clock drawing score	0.09 ± 0.18	0.28 ± 0.15	0.19 (−0.17 to 0.54)	0.19 (−0.16 to 0.54)
Memory				
Immediate recall, 15-WVLT score	0.42 ± 0.11	0.13 ± 0.18	−0.29 (−0.72 to 0.13)	−0.25 (−0.67 to 0.17)
Delayed recall, 15-WVLT score	0.74 ± 0.15	0.46 ± 0.28	−0.28 (−0.90 to 0.35)	−0.23 (−0.85 to 0.39)
VAT score	0.10 ± 0.04	0.19 ± 0.06	0.10 (−0.05 to 0.25)	0.10 (−0.06 to 0.25)
Executive function				
TMT B-A, s[c]	−4.26 ± 2.90	9.03 ± 4.71	13.29 (2.30 to 24.28)[d]	13.94 (3.76 to 24.12)[d]
SCWT III-II, s[c]	−6.21 ± 1.80	0.13 ± 3.18	6.35 (−0.87 to 13.57)	5.31 (−1.69 to 12.31)
Psychomotor speed				
LDST, correct/min	0.06 ± 0.25	−0.36 ± 0.42	−0.42 (−1.37 to 0.54)	−0.43 (−1.36 to 0.51)
TMT A, s[c]	−1.62 ± 1.27	−1.07 ± 2.00	0.55 (−4.15 to 5.24)	0.25 (−0.98 to 4.46)
SCWT II, s[c]	−2.38 ± 0.78	−2.58 ± 1.32	−0.20 (−3.23 to 0.83)	−0.57 (−3.58 to 2.43)
Health-related Quality of Life[b]				
RAND-36 physical summary score	−0.52 ± 0.45	−1.04 ± 0.72	−0.52 (−2.20 to 1.15)	−0.48 (−2.13 to 1.18)
RAND-36 mental summary score	−0.45 ± 0.47	0.76 ± 0.74	1.21 (−0.52 to 2.93)	1.25 (−0.46 to 2.95)

Figures are presented as mean annual change (SE) for apathy symptoms and mean difference in annual change (95% CI) for difference in annual decline. Outcome data was completely missing for FFI, n = 1 (0.6%); walking speed, n = 10 (5.6%); WVLT delayed, n = 2 (1.5%); VAT, n = 1 (0.6%); TMT B-A, n = 5 (2.8%); SCWT III-II, n = 4 (2.2%); LDST, n = 1 (0.6%); TMT-A, n = 1 (0.6%); SCWT II, n = 2 (1.1%); RAND-36, n = 4 (2.2%).
Abbreviations: FFI, Fried Frailty Index; GARS, Groningen Activity Restriction Scale; LDST, Letter Digit Substitution Test; MMSE, Mini-Mental State Examination; SCWT, Stroop Color Word Test; TMT, Trail Making Test; VAT, Visual Association Test; 15-WVLT, 15-item Word Verbal Learning Test.
[a]Adjusted for age, sex, and high education level.
[b]The mean number of measurements per outcome varied from 2.25 ± 1.32 SD to 2.45 ± 1.38 SD.
[c]Higher scores mean less performance.
[d]Statistically significant values.

Association of Apathy With Risk of Mortality

Figure 1 presents a Kaplan-Meier survival curve showing higher mortality among patients with apathy symptoms. The crude hazard ratio [HR] was 1.88 ([95% CI, 1.05-3.36], P = 0.033), after adjustment for age, sex, and high education level (HR, 2.32 [95% CI, 1.29-4.17], P = 0.005). Additional adjustment for history of diabetes mellitus or vascular disease did not change the estimates (Table S4). All independent variables met the criteria for the proportional hazard assumption.

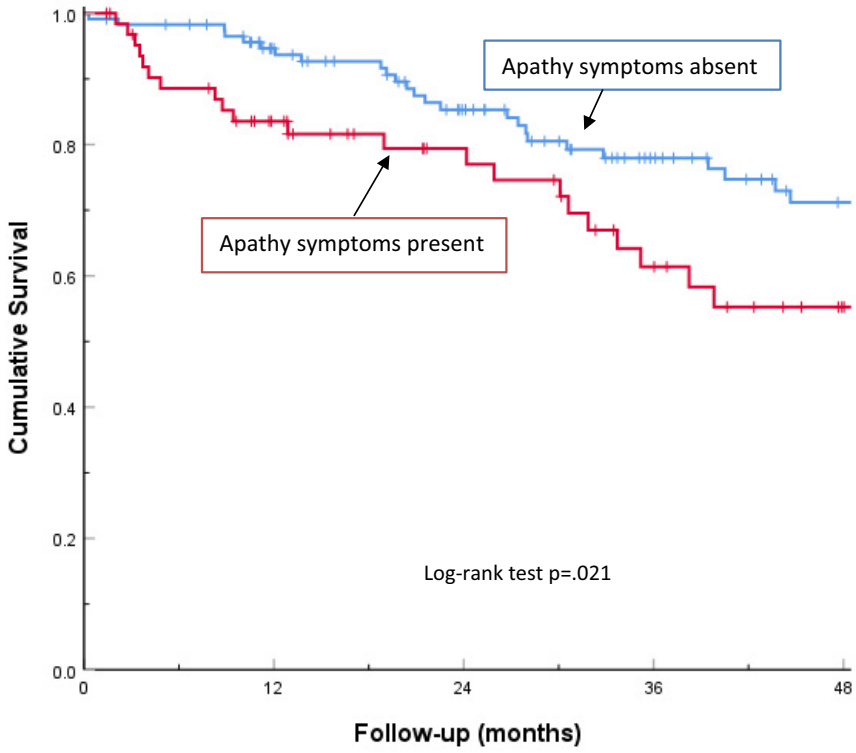
Sensitivity Analyses

To distinguish the associations of symptoms of apathy from depressive symptoms, we repeated our analysis by comparing the persons with isolated apathy symptoms with those who had no apathy symptoms. We found comparable estimates, both cross-sectionally (Table S2: physical functioning [frailty, GARS score, walking speed], executive functioning [TMTΔ], and physical HRQoL were more impaired in isolated apathy patients compared with those who had no apathy symptoms) and longitudinally (Table S3). Mortality risk was higher in patients with isolated apathy symptoms (crude HR, 2.37 [95% CI, 1.21-4.63]; adjusted HR, 2.53 [95% CI, 1.29-4.96]), similar to the main analysis.

Discussion

The main findings of this study were 3-fold. First, symptoms of apathy were present in 36% of older patients with CKD. In half those patients the symptoms of apathy were unrelated to symptoms of depression. Second, presence of apathy symptoms was associated with lower physical and cognitive functioning and HRQoL at baseline. Third, presence of apathy symptoms was associated with a 2-fold higher risk of mortality over 4 years.

Our findings on the occurrence of apathy symptoms are in concordance with previous smaller CKD studies that have reported an occurrence of apathy of one-fifth in all stages of the CKD adult population and up to two-thirds in



Number at risk:

No apathy	116	97	76	53	39
Apathy symptoms	64	45	33	22	12

Figure 1. Cumulative mortality depending on the presence and absence of apathy symptoms in older patients with chronic kidney disease.

the adult dialysis patients.[14,36] The prevalence of apathy symptoms in our cohort was somewhat higher compared with previous estimates from community-dwelling older population cohorts[22,30,37] and older primary care patients.[29-31] As in other studies, symptoms of apathy were related to depressive symptoms,[15,16,30] but they occurred without depressive symptoms in half the cases.[22,29,30] We found that apathy symptoms were associated with a vascular cause of kidney disease. This fits the vascular apathy hypothesis that apathy is caused by cerebral small vessel disease[7] and is in line with our previous finding in a subset of this cohort in which patients with a history of vascular disease showed more cerebral white matter hyperintensities on magnetic resonance imaging.[27]

Our findings on physical functioning are in line with other studies in community-dwelling older persons showing more frailty and lower functional status among patients with apathy symptoms compared with those who had no apathy symptoms.[38-40] Although larger longitudinal studies in older adults and Alzheimer's disease patients found more decline in physical functioning in patients with apathy symptoms,[37,41,42] in our cohort we could not confirm a faster decline of dependency and physical capacity for these patients. The outcomes on cognitive functioning (visuoconstructive abilities, memory, and executive function) were consistent with earlier findings on dysfunction in critical subcortical-frontal brain circuits.[18,43] Recent systematic reviews have described the lack of evidence on apathy and cognitive decline,[5,44] but a longitudinal relationship to incident mild cognitive impairment and dementia was described.[3,5] In concordance, we found a faster decline in executive functioning in patients with apathy symptoms in our cohort, but we found no difference in other cognitive domains for patients with apathy symptoms, supporting the antithesis.

We found lower physical and mental HRQoL in those with apathy symptoms, as did other studies in stroke patients and nursing home residents.[45,46] Survival outcomes of our study were more prominent and exceed (albeit overlapping confidence intervals) the 47% higher risk for persons with apathy symptoms from a recent meta-analysis among community-dwelling older people.[22] Although residual confounding is likely, a history of diabetes mellitus and vascular disease did not explain the association between apathy symptoms and increased mortality risk in our population. Furthermore, our analysis was based on a

single measurement of apathy symptoms at baseline. A patient manifesting apathy symptoms without depressive symptoms may have developed these over time or have gone through other physical and emotional events that could have contributed to the poor outcomes associated with the presence of apathy symptoms. Overall, our findings in CKD are thus consistent with other older populations.

Apathy has a particular high burden on patients and relatives,[19-21,47] and our results therefore suggest that apathy is a potentially relevant phenomenon and highlight several clinical implications for future nephrology practice. First, clinical awareness to distinguish symptoms of apathy from depressive symptoms in CKD may be desirable. Both symptoms of depression and apathy are prevalent in approximately one-third of CKD patients[8] but exist to a large extent independently of each other. One would want to prevent treating patients for depression if apathy is the problem; antidepressants may have limited effects on apathy.[48] Unfortunately, evidence on apathy treatments is scarce and may be aimed at alleviating patient disability rather than pharmacological interventions.[18,48] There are no well-powered randomized, controlled trials demonstrating any treatment effect in apathy. Also, with emerging evidence for the hypothesis of vascular apathy, studies toward depression in CKD populations may need to consider taking apathy into account as a potential common cause or confounding variable.

Second, clinical awareness for the presence of apathy symptoms may be relevant for the treatment of older CKD patients, both in the decision-making process for their upcoming choice of kidney replacement therapy and in the guidance of therapy adherence. Deficits in effort-based decision making have been associated with apathy in patients with cerebral small vessel disease.[49] One may postulate that the loss of motivation and reduced goal-directed behavior may require a different approach compared with patients who are not experiencing apathy symptoms.[43]

Third, the presence of apathy symptoms might be an indicator of other physical and cognitive impairments. Together with the higher mortality risk among patients with apathy symptoms, it highlights the vulnerability of this patient group. The predictive value of apathy symptoms on cognitive decline may be a topic for future research in larger CKD populations. If such studies are more conclusive, apathy itself might be of interest to include in geriatric evaluation.

Strengths of our exploratory study are the unique study population, relevant outcomes for older CKD patients, and the extensive cognitive and physical tests that were conducted annually during a 4-year follow-up. This provided the opportunity to explore a broad range of physical and cognitive outcomes and progression over time. The study also had limitations. First, patient inclusion in our study cohort might have been selective, potentially limiting the generalizability of our results. Because the study was initiated from a routine care perspective to identify cognitive deficits, on the one hand, patients were more likely to be included when having a reason for geriatric workup. On the other hand, patients with worse conditions might also have been less likely to participate. Second, we conducted an observational study, and we could not make any causal interpretations. Residual confounding remains a possible explanation for the associations that were found. Nevertheless, our findings are a first step toward insights into relationships between apathy symptoms and outcomes. Third, our results are confined to the use of the GDS-3A instrument, which was used to define apathy symptoms, and dichotomization of its presence. The GDS-3A has shown high specificity and low sensitivity.[31] Because GDS-3A items closely connect to functional disability,[50] apathy symptoms might rather be an indicator of a less active and home-bound life due to an individual's chronic illness. Future research should further disentangle apathy as an independent entity by using other more dedicated instruments.[51] Fourth, we included many outcome parameters in our analyses, which might have been a risk for a statistically significant result purely by chance (ie, type I error). However, all outcomes pointed consequently in the direction of lower functioning for patients with apathy symptoms.

In conclusion, our study reveals that symptoms of apathy are highly prevalent in our cohort of older CKD patients, often independent of depressive symptoms. Because of the relation of apathy symptoms with mortality, physical and cognitive status, and HRQoL, symptoms of apathy could be a potentially relevant clinical entity in care for advanced CKD patients.

Supplementary Material

Supplementary File (PDF)

Figure S1: Boxplots of distributions of physical and cognitive functioning and health-related quality of life measurements over time.

Table S1: Baseline characteristics of patients with isolated apathy symptoms and combined apathy and depressive symptoms.

Table S2: Baseline associations of the presence of isolated apathy symptoms versus absence of apathy symptoms with measures of physical functioning, cognition, and depressive symptoms.

Table S3: Annual change in physical and cognitive functioning during follow-up for older CKD patients with isolated apathy symptoms versus absence of apathy symptoms.

Table S4: Analysis of presence of apathy symptoms on mortality risk.

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Apathy Symptoms, Physical and Cognitive Function, Health-Related Quality of Life, and Mortality in Older Patients With CKD

Setting & Participants	Analysis	Findings
Observational study **5 nephrology outpatient clinics in the Netherlands** **N = 180 patients** • Median age: 75.5 years • 67% male • eGFR ≤ 20 mL/min/1.73 m^2 **4-year follow-up**	**Apathy symptoms present when Geriatric Depression questionnaire subscale 3A (GDS 3A) ≥ 2 points**	**Apathy symptoms were present in 36% of patients (N = 64), of whom 50% (N = 32) had no depressive symptoms**

Presence of Apathy Symptoms Associated With:

Outcomes	*Cross-Sectional*	*Longitudinal*
Physical Functioning	↑ Frailty ↑ Dependence ↓ Capacity	No difference in progression detected
Cognitive Functioning	↓ Visuo-construction ↓ Memory function	
Health-Related Quality of Life	↓ Mental HRQoL - 7.1 ↓ Physical HRQoL - 9.5	
Mortality Risk	↑ **HR** 2.3 (95% CI 1.3-4.2)	

CONCLUSION: Apathy symptoms are associated with lower physical and cognitive status, lower HRQoL, and increased mortality in older patients with advanced CKD.

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