Apathy: Risk Factor for Mortality in Nursing Home Patients

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OBJECTIVES: To determine the prognostic value of apathy for mortality in patients of somatic (SC) and dementia special care (DSC) nursing home (NH) units.

DESIGN: Longitudinal design, secondary analyses of a 2-year, cluster-randomized trial with six measurements, approximately 4 months in between.

SETTING: SC and DSC-units of Dutch NHs.

PARTICIPANTS: NH-patients of seventeen SC-units (n = 342) and sixteen DCS-units (n = 371).

MEASUREMENTS: Data were available for 713 NH-patients, 266 of whom died during the study. Apathy was assessed using the 10-item Apathy Evaluation Scale (AES-10) and applied as categorical variable using known cut-off scores as well as dimensional variable. Additionally, depressive symptoms were assessed using the Cornell Scale for Depression in Dementia.

RESULTS: Mixed effects cox models using the coxme package in R revealed a higher risk of mortality between two measurements, if apathy was present (hazard ratio (HR) = 1.77; 95% confidence interval (CI] = 1.35–2.31, $P < .001$). Results remained significant (HR = 1.64; 95% CI = 1.23–2.19, $P < .001$) when controlled for depressive symptoms. DSC-units and SC-units did not differ ($P > .05$) in the effect of apathy on mortality. Male gender (HR = 1.67; 95% CI = 1.23–2.27, $P < .001$), and higher age in years (HR = 1.06; 95% CI = 1.04–1.08, $P < .001$) were also predictors of mortality. Regarding apathy as a dimensional construct, one standard deviation increase of AES-10 scores was associated with a 62% increase of mortality risk (HR = 1.62, 95% CI = 1.40–1.88, $P < .001$).

CONCLUSIONS: Apathy was associated with mortality over a 4-month period in NH patients, even when controlling for depression. These data suggest that screening and treatment strategies for apathy should be developed for this patient population. **J Am Geriatr Soc 65:2182–2189, 2017.**

Key words: mortality; apathy; risk factor; depression; nursing home; somatic; dementia care

Apathy is common in nursing home (NH) patients with dementia and is repeatedly found to be the most prevalent neuropsychiatric symptom.[1–3] Apathy is defined by diminished or lack of motivational, goal-directed behavior, and a lack of cognition and emotional affect. Apathy leads to reduced interest and participation in the main activities of daily living, diminished initiative, early withdrawal from initiated activities, indifference, and flattening of affect.[4,5] Over the last two decades, more scientific knowledge has become available about specific fronto-subcortical systems in the brain that may be highly involved in apathy.[6,7] Disruptions in these systems are found in patients with frontal lobe damage resulting from, for instance, (early-onset) dementia, traumatic brain injury, stroke, or multiple sclerosis.[8–10] Fronto-subcortical circuits also play an important role in neurological disorders involving the basal ganglia, including Parkinson's disease and Huntington's disease.[9,11,12] The neurodegenerative diseases and acquired brain injuries mentioned here are highly prevalent in patients receiving long-term somatic care (SC), and the widespread clinical manifestation of apathy in SC-units of NHs is thought to be related. However, in contrast to the abundance of research into apathy in patients within dementia special care units (DSC), research into apathy in SC-patients without dementia is rare.

Furthermore, although apathy is common in NH-patients and is associated with adverse outcomes including poor treatment response, more rapid cognitive decline, increased reliance on caregivers, and earlier institutionalization,[10,13–17] it is rarely considered a problem by professional staff in that setting.[18,19]

Interestingly, only a few studies have investigated the prognostic value of apathy for mortality, and the findings are inconsistent. Hölttä et al.[20] found that apathy had a

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negative effect on survival rates in acute geriatric wards and NHs and predicted mortality after controlling for age, gender, delirium, and dementia (HR = 1.89, 95% CI 1.24–2.89; $P = .003$). On the other hand, in their study of elderly people living in the community or in NHs, Okura et al.[21] found that agitation, depression, and delusion–but not apathy–were of independent prognostic value for mortality. Furthermore, Peters et al.[22] found that earlier death was associated with psychosis, affective symptoms, and agitation/aggression, but not with apathy. However, these studies operationalized apathy as categorical construct, with apathy being either present or not. This simple dichotomization of apathetic behavior does not reflect the nosological complexity of apathy, which could also be considered a dimensional concept varying from diminished interest to total absence of initiative, goal-directed behavior, emptiness of thoughts, and emotional blunting.[23] Apathy, loss of interest or pleasure, is a principal symptom used to diagnose depression, even when depressed mood is not present.[24,25] While various studies support the discrimination between apathy and depression,[5,26,27] a combination of different and overlapping risk factors necessitates taking depression into account when studying apathy.

Since apathy is very common in NH-patients and may lead to a poor prognosis, clear insight into its risk for mortality is needed, and NH-staff need to understand this risk.

As apathy has rarely been studied in patients without dementia living in SC-units, and the question of whether apathy should best be considered as a dimensional or a categorical variable has not yet received much attention, the aims of the current study are: (1) exploring the relationship between apathy and mortality in NH-patients and to investigating whether there is a difference in the prognostic value of apathy for mortality in patients of SC-units and in patients of DSC-units, and (2) exploring the relationship between apathy and mortality for apathy both as a categorical and dimensional variable.

METHODS

Design, Participants, And Ethics

Data is derived from the Act in Case of Depression (AiD) study, a Dutch stepped-wedge cluster-randomized trial with five groups and six time points (T0–T5) with approximately 4 months between measurements, thus providing longitudinal data.[28] A stepped-wedge design is a crossover design with repeated measurements and randomization of time points for crossing over from the control condition to the intervention condition. This enables comparisons between and within clusters. All clusters were in the control condition at baseline (T0). A randomly selected group of clusters implemented the intervention shortly after T0. Other groups crossed over after T1, T2, T3, and T4, respectively. At T5, all clusters were in the intervention condition. In the intervention condition, a program containing depression assessment procedures and multidisciplinary treatment (activating strategies, psychotherapy, medication) was introduced. The duration of the intervention at T5 varied from 4 months (group five) to 20 months (group one). Details of the design and methods of the original study and its findings have been reported elsewhere.[1]

Data were collected from May 2009 to April 2011 on 16 DSC-units and 17 SC-units within organizations of the Nijmegen University Nursing Home Network (UKON), and collaboration between 15 care organizations and the Department of Primary and Community Care of the Radboud University Medical Centre, Nijmegen. The Medical Ethics Committee (CMO Arnhem-Nijmegen) rated the AiD study.

Procedure

At the start of the parent study all patients residing on participating units at that time were approached for participation. Written informed consent was obtained from each patient or a relative/representative when a patient could not provide informed consent. Only subjects with informed consent were included in the study. Individual participants were assessed at each measurement point, providing longitudinal data, up to six measurements per participant if the participant started at T0 and continued the study through T5. During the study period, newly admitted patients were included and their baseline assessment was performed at the next measurement point. Apathy and depressive symptoms were assessed by interviewing the nursing staff. Cognition was assessed in the participants who could be tested.[29] For the current analyses, participants were excluded if only one measurement was available without further assessments. If a participant died, moved, or withdrew informed consent between two measurements, the already performed measurements were included in the analyses (flow chart, Figure 1). No data were available on whether patients were in a palliative state; therefore, to exclude the influence of a possible palliative state and increase validity, we excluded a measurement if a patient died within 10 days after the measurement.

Measurements

Sociodemographic Characteristics and Mortality

For all patients, data were available on age, gender, date of institutionalization, as well as type of care unit for the 20-month duration of the study. Date of death was obtained from the medical file.

Apathy: Abbreviated Apathy Evaluation Scale (AES-10)

Apathy was determined using the 10-item Apathy Evaluation Scale (AES-10).[4,30] The 10 items of the observation scale all give an example of apathetic behavior in the NH-population. The response categories vary from 1 (not at all characteristic) to 4 (very characteristic), resulting in a total sum score ranging from 10 to 40. To conceptualize apathy, we used both a continuous measure (AES-10 total score, a higher score indicating more apathetic behavior) and a categorical entity (apathy is present or not). A cut-off score of >21 was used in patients of SC-units and of >29 in patients of DSC-units based on the validation study of Leontjevas et al.[31] which showed cut-off points for distinguishing those with aipathy from those without apathy.

Depressive Symptoms: Cornell Scale for Depression in Dementia (CSDD)

The CSDD consists of 19 items; each rated as 0 (absent), 1 (mild), or 2 (severe). A higher total-sum score indicates more severe depressive symptoms. The scale was validated in patients with dementia[32] and in NH-patients with and without dementia.[33]

Cognitive Functioning: Mini-Mental State Examination (MMSE)

For those patients testable, the standardized MMSE[34] was administered with the patient during a structured interview for assessing global cognitive functioning. Scores range from 0 to 30, with ≥24 considered normal cognition and <24 considered impaired cognition.

Other Variables

Other factors known to be related to mortality such as functional status, neuropathology, type of dementia, cognition, and comorbidity were accounted for using the proxy variable 'type of unit.' Based on these factors, the patient characteristics on SC and DSC-units differ considerably. Overall in SC-units, caregiving is centered more on symptoms due to physical frailty, and in DSC-units, it is centered on cognitive and behavioral symptoms due to dementia.[35,36]

Statistical Analysis

Longitudinal data represent up to five repeated measurements of survival predictors. Survival/death was registered within the period between the measurements or, for the 5th measurement, before the end of the study. If data for apathy or depression scores were missing in a patient in between other measurements that were available, the mean score of the data available on the nearest time point before and after the missing time point were imputed (CDSS observations n = 132, AES n = 73). When two successive measurements were missing, data were adjusted by calculating the expected value in between two available measurements.

Descriptive statistics were generated for the total sample and for patients of SC-units and DSC-units separately. Patients of SC and DSC-units were compared on gender, age, apathy (as a categorical or dimensional construct; AES-10), CSDD, and MMSE. To analyze differences between patients in SC and DSC-units, paired *t*-tests for dimensional variables, and χ^2-tests for categorical variables, were performed. By calculating cluster means, all numbers were adjusted for clustering.

The coxme package in the R statistical environment was used for building multi-level mixed effects cox models[37] for patients clustered in NH-units, and measurements clustered within patients. At the patient level, we used days between available time-point measurements and, if relevant, between the last measurement and date of death. All models were adjusted for age and gender. We built models with apathy as a categorical and dimensional predictor (standardized score), respectively. We then adjusted the models for CSDD (standardized score). To explore the difference between DSC and SC-units, we built additional models with the type of unit and its interaction with apathy. We did not adjust the models for the status intervention/control because being in the intervention condition or control condition did not improve the fit of models predicting mortality (e.g. $\chi^2(1) = 0.740$, $P > .05$ for comparing models with AES-score adjusted and not adjusted for the intervention condition).

Sensitivity analyses that adjusted for cognitive impairment were performed in a subsample of patients (n = 545) with available MMSE-scores.

A Kaplan–Meier plot was generated to visualize survival probabilities for patients with and without apathy in SC-units and DSC-units.

RESULTS

The present study includes data of 713 patients, 266 of who died during the study (see flowchart, Figure 1).

As Table 1 shows, most of the patients were female (n = 484, 68%), both in SC's (n = 220 (64%)) and DSC's (n = 264 (71%)). Patients in SC-units were significantly younger (77.8 (SD 13.1)) than patients in DSC-units (83.1 (SD 6.9)). At baseline, if regarded as categorical construct, half of all patients showed apathy (n = 366, (51%)). Mean AES-10-scores were lower in patients of SC-units (SC 23.2 (SD 8.5)) than in patients of DSC-units (29.1 (SD 7.6)). Patients in SC-units had higher levels of cognitive function by MMSE than patients in DSC-units (SC, 19.9 (SD 7.3); DSC, 8.5 (SD 7.6)).

Apathy As A Categorical Construct

Mixed effects cox models revealed a higher risk of mortality in the total sample if apathy (categorical) was present (HR = 1.77, 95% CI = 1.35–1.81; $P < .001$; Table 2). Although apathy seemed more strongly related to mortality in SC-patients (HR = 2.24, 95% CI = 1.44–3.47, $P < .001$) than in DSC-patients (HR = 1.53, 95% CI = 1.09–2.15, $P = .014$), the difference between unit types in risk of mortality was not significant ($P = .18$; Figure 2).

Adjusting for depressive symptoms (CSDD), the results remained significant in the total sample (Table 2, model 2; HR = 1.64, 95% CI = 1.23–2.19, $P < .001$). Also, although the point estimations of the Hazard ratio decreased slightly after the correction for the CSDD, the results remained significant in both unit types and the 95% CI before and after the correction overlapped.

Apathy As A Dimensional Construct

Using a continuous measure of apathy, we found that one SD increase of AES-10 scores was associated with a 62% increased mortality risk (HR = 1.62, 95% CI = 1.40–1.88, $P < .001$). Although apathy as a dimensional construct seemed more strongly related to mortality in somatic patients (HR = 1.79, 95% CI = 1.44–2.23, $P < .001$) than in patients in DSC-patients (HR = 1.55, 95% CI = 1.25–1.91, $P < .001$), the difference between SC-units and DSC-units was not significant ($P = .34$).

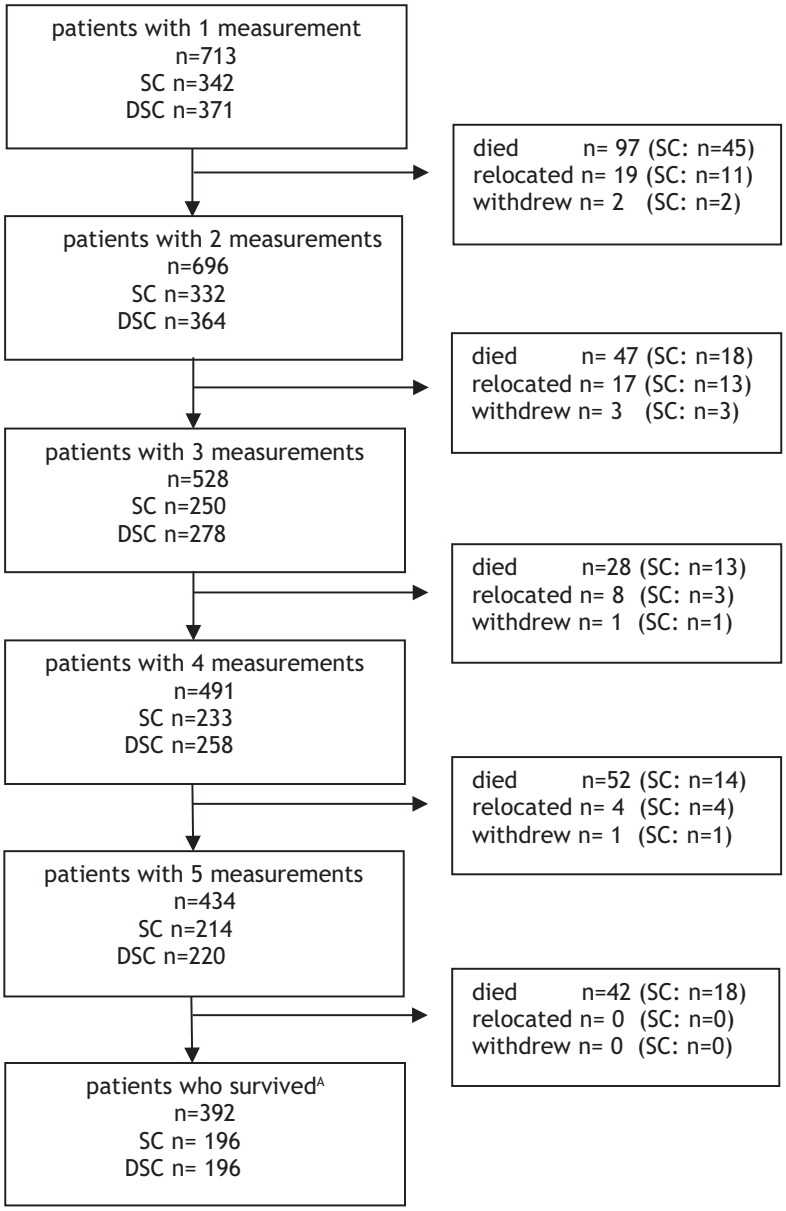

Figure 1. Flow chart measurements of patients. [a]patients who were alive at the end of the study.

After correction for depressive symptoms, the point estimations of the Hazard ratio in SC and DSC-units seemed to decrease slightly, but the prognostic value for apathy as a dimensional construct remained significant (HR = 1.56, 95% CI = 1.33–1.83), and the 95% CI before and after the correction overlapped.

Of the covariates, male gender (HR = 1.67; 95% CI = 1.23–2.27, $P < .001$), and older age (HR = 1.06, 95% CI = 1.04–1.08, $P < .001$) were significant predictors of mortality in all mixed models (numbers represent model 1, apathy as a categorical construct).

Sensitivity analyses in a subsample of patients with available MMSE-scores showed that adjusting for MMSE decreases the point estimation of the effect of apathy (Appendix S1). For example, HR decreased from 1.63 (95% CI = 1.39–1.91, $P < .001$) to 1.48 (95% CI = 1.23–1.78, $P < .001$) in a model with AES-10 as predictor after correcting for MMSE. However, it could be concluded that the unique effect of apathy remains after the correction for MMSE because the 95% confidence intervals of the HR's overlap for models before and after correcting for MMSE, and most models showed significant coefficients for apathy (except for apathy as a dichotomous variable in DSC-units).

DISCUSSION

In this study, apathy was found to be associated with highly increased mortality in SC-patients and in DSC-patients in Dutch NHs when the construct was conceptualized both as a categorical and as a dimensional variable. Apathy significantly increased the risk of dying in the total sample. When regarded as categorical construct, apathy was present in half of the NH-patients, implying that it is a very common neuropsychiatric phenomenon in patients of both SC-units and DSC-units. Although apathy seemed to

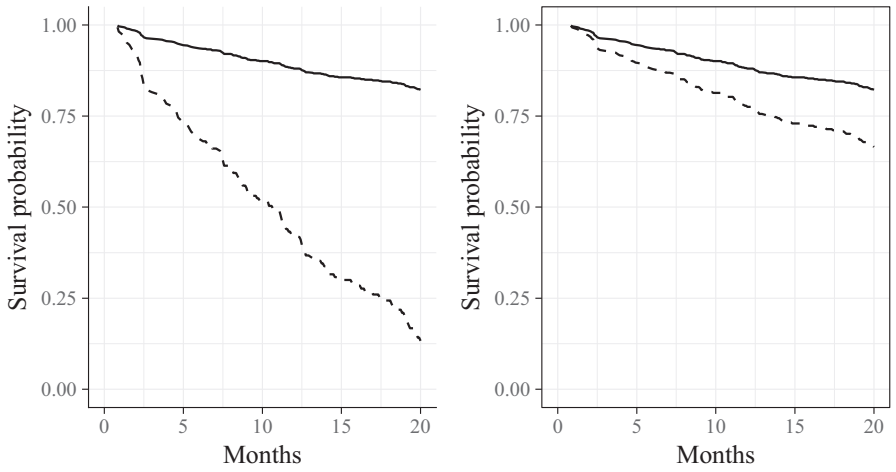

Figure 2. Survival probability in months for patients of SC (left) and DSC (right), for patients with apathy (dotted line) and patients without apathy (black line), apathy as categorical construct.

Table 1. Patient characteristics at their first measurement, n = 713

	Somatic N = 342	Dementia N = 371	*P*	Total N = 713
Gender (female) n (%)	342 (64)	371 (71)	.051	713 (68)
Age (years) (SD)	77.8 (13.1)	83.1 (6.9)	<.001	80.6 (10.7)
Apathy (categorical)[a] n (%)	182 (48)	184 (52)	.334	366 (51)
Apathy (dimensional) (AES10) (mean, (SD)/n)	23.2 (8.5)	29.1 (7.6)	.004	26.2 (8.6)/709
Cognition (MMSE) (mean, (SD)/n)	19.9 (7.3)	8.5 (7.6)	.044	14.2 (7.6)/545
Depressive symptoms (CSDD) (mean, (SD)/n)	9.5 (7.6)	9.6 (6.9)	.020	9.6 (7.3)/697

[a]Apathy (categorical): AES10 cut-off scores of >29 in dementia patients and >21 in SC patients.[33]

Apathy (dimensional): standardized score on the AES10. Cognition: score on the MMSE. Depressive symptoms: standardized score on the CSDD. All numbers are adjusted for clustering.

Dementia: patients of Dementia Special Care units (DSC); Somatic: patients of Somatic Care Units (SC). *P*: significance for the difference between patients DSC and SC. *T*-test, $P < .05$; $P < .001$.

Table 2. Presence of Apathy and Risk of Dying in Somatic Care and Dementia Special Care

	Somatic (SC)		Dementia (DSC)		Total		SC Versus DSC
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	*P*
Apathy (categorical)							
Model 1	2.24 (1.44–3.47)	<.001	1.53 (1.09–2.15)	.014	1.77 (1.35–2.31)	<.001	.18
Model 2	2.08 (1.29–3.33)	<.05	1.44 (1.01–2.06)	<.05	1.64 (1.23–2.19)	<.001	.22
Apathy (dimensional)							
Model 1	1.79 (1.44–2.23)	<.001	1.55 (1.25–1.91)	<.001	1.62 (1.40–1.88)	<.001	.34
Model 2	1.73 (1.37–2.19)	<.001	1.48 (1.18–1.84)	<.001	1.56 (1.33–1.83)	<.001	.32

Model 1, not corrected for the effect of CSDD; Model 2, adjusted for the effect of CSDD. All models corrected for age and gender.

Apathy (categorical): cut-off scores of >29 in dementia patients and >21 in SC patients; Apathy (dimensional): AES-10 sum scores.

Hazard Ratios (HR) using coxme package in R with depression symptoms as the dependent variable.

SC=somatic care; DSC=dementia special care; *P*-values in Mixed Effects Cox Models (coxme package in R).

be more strongly related to mortality in somatic patients than in patients of DSC-units, we did not find a significant difference between the unit types regarding the mortality risk. Also, when the analyses accounted for co-occurring depressive symptoms, a strong and significant relationship remained between apathy and mortality. This result differs from the findings of Okura et al.[21] and Peters et al.,[22] who found that assessing each individually symptom of the Neuro Psychiatric Inventory (NPI) depression, psychosis, and aggression/agitation, but not apathy, were associated with greater risk of death. Different instruments for assessing apathy and differences in patients and neuropsychiatric symptoms that were examined, may explain the difference with our results. Regarding apathy—both as categorical and as a dimensional construct—in this study we found that even a small increase of one standard deviation in

apathy reflects a greater risk of dying. This is in line with a study by Vilalta-Franch et al.,[17] who found that in Alzheimer's disease, apathy as a syndrome predicts increased mortality. Apathy may thus point to poor prognosis in NH-patients. Moreover, when the analyses accounted for co-occurring depressive symptoms, apathy still appeared to be a significant predictor of mortality, thereby highlighting the independent association between apathy and mortality. This underlines that apathy and depression are not the same. These findings are consistent with previous research reporting that apathy independently predicts mortality.[17,20] It also underpins the need for consensus on assessment, diagnostic, and treatment guidelines as stated by Mulin et al.,[38] and Starkstein & Leentjes[39] so that apathy can be adequately detected and treated.

The current study has strengths and limitations. To our knowledge, it is the first to examine the association between apathy and mortality in a large sample with multiple measurements of patients of SC-units and DSC-units, thus providing insight into similarities and differences between those patient groups. Additionally, apathy and depression are mostly assessed in research as categorical constructs using the NPI,[40] where in this study we used other valid questionnaires to specifically assess apathetic behavior (AES-10) and depressive symptoms (CSDD).

Several factors are individually associated with mortality in frail elderly people and NH- patients, including comorbidity, physical functioning, neuropathology, cognitive decline, psychotropic drug prescription, and type of dementia.[20,21,41] A potential limitation of this study is that we did not correct for each possible confounder. We used a proxy measure (the type of care-unit) to account for these variables. Within a smaller subset of patients with MMSE-data available, we found that, when accounted for cognition, the prognostic value of apathy as a dimensional construct on mortality remained significant. Although previous studies show that apathy is associated with severity of cognitive decline and cognitive impairment,[5,17] the results in this study point to the prognostic value of apathy in mortality being more strongly present in SC-units than in DSC-units. That this difference was not significant, may indicate that some of the characteristics common to patients in SC-units[8,9,11] and DSC-units[10,42] involve impairments in the fronto-subcortical brain circuits where executive cognitive functioning is mediated and simple ideas, movements, and actions are transitioned into complex goal-directed behaviors.[43,44] Yet, the impact of cognitive deficits on the findings may have been underrated as the adjustment for MMSE-scores regarded a subsample that may not have included those participants who were most severely impaired and at a higher risk for mortality. Also, functional disability and anti-psychotic drug use are known to be related to mortality and are not accounted for separately in this study because these were not assessed in the parent study[3,17] Functional impairment, however, has been found to be more strongly related to apathy than to cognitive deficits,[5,45] but little is known about the underlying potential mechanism, suggesting that further research is required to assess the influence of functional impairment on the relationship between apathy and mortality. Known side effects of psychotropic drugs include extrapyramidal symptoms and drowsiness/sedation and, like cognitive decline and delirium, they may enhance frailty and apathy, while increasing the risk of developing pneumonia and malnutrition, which are also associated with mortality in nursing homes.[3,17,20,46,47]

Another limitation may be that the analyses were constrained by the design of the parent study, an intervention study, and the effect of the intervention on the relationship between apathy and mortality could not be fully assessed. Although we did explore the possible effect of being in the intervention condition and no significant effect was found, it may have been better to use data from patients in the same condition. However, because patients waited to crossover to the intervention condition given the within-between subject design of the parent study, this would have resulted in survival bias favoring the intervention condition.

Our results underpin that apathy is a common neuropsychiatric phenomenon with serious adverse outcomes in NH-patients and that it has important implications for patients, their families, and NH-staff. Despite increased interest in the treatment of apathy, results of intervention studies are inconsistent and no treatment has yet been established. Recent research has targeted medical treatment,[48] deep brain stimulation of the subthalamic nucleus,[49] and psychosocial treatment (cognitive rehabilitation, psychotherapy, activity, and occupational therapy).[50–52]

To increase awareness and identification and because apathy is still rarely identified as a problem in NHs, further research is needed.[18,19] Effective screening and treatment strategies should be developed and analyzed for their effects on reducing apathy in patients and improving quality of life (QoL). Surprisingly, little is known about the relationship between apathy and QoL. Few studies have been conducted with inconsistent results.[5,53,54] Although in this study the prognostic value of apathy for mortality was not influenced by patients receiving multidisciplinary treatment (activity strategies, psychotherapy, and medication), this treatment was found to reduce apathy in patients with dementia, which was mainly attributable to activating strategies.[50] These promising findings can direct further investigations that focus on the relationship between apathy and QoL and adjusting environmental factors in NHs through enhancing patient engagement in activation programs. In the meantime, daily practice should focus on improving QoL and advanced-care planning when apathy is present in a NH patient.

CONCLUSION

Apathy is present in half of the patients of both SC-units and DSC-units and is associated with highly increased risk for mortality, also when accounting for depressive symptoms. Considered as both a categorical and dimensional construct, apathy reflects poor prognosis in NH-patients. When regarded as a dimensional variable, even a small increase of apathy reflects a greater risk of dying. No effective treatment for apathy has yet been established. Further research is needed on effective screening and treatment for apathy and enhancing professional caregivers' awareness of apathy as a poor prognostic sign. The presence of apathy in NHs should become a point of particular

concern in daily care and should initiate establishing goals of care to improve quality of life and advanced care planning in the context of decreased life expectancy.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Presence of apathy and risk of dying in somatic care and dementia special care in a subsample with MMSE-scores available (n = 545)

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