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Original Research

Subjective Cognitive Decline as a predictor of Frailty in older adults: Hellenic Longitudinal Investigation of Aging and Diet study (HELIAD)

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Abstract

BACKGROUND: Subjective cognitive decline (SCD) is a self-evaluation of cognitive impairment, in the absence of observed objective cognitive deficits on a neuropsychological assessment. Frailty refers to a multidimensional syndrome where the individual has poor health including falls, disabilities, hospitalization, and vulnerability. Both terms are associated with cognitive decline and increased incidence of dementia. The present longitudinal study explored whether the detection of SCD can predict the development of frailty over time.

METHODS: The Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) is an epidemiological, population-based study. From the original testing sample of 1,984 older Greek individuals (≥65 years old), 1,121 remained in the longitudinal analysis. Participants diagnosed with frailty, Mild Cognitive Impairment (MCI), dementia, severe depression, and anxiety, in the baseline assessment were excluded from the analysis (n=146), resulting in a total sample of 975 participants. The average follow-up interval was 3.1 years (SD=0.84 years). SCD was assessed in the baseline assessment with a series of eighteen questions. The questions regarding SCD were categorized according to cognitive domains. Frailty was assessed according to a phenotypic-physiologic (Fried's definition) and a multidomain approach (Frailty Index). Univariate and multivariate Cox regression analyses were used for exploring the role of SCD in developing frailty.

RESULTS: The proportion of individuals with frailty according to Fried's definition was greater compared to the Frailty Index. At follow-up according to Fried's definition, a greater proportion of cases with frailty was found in those who reported SCD complaints regarding orientation (OD) (HR=3.12 95% CI:1.45-6.73 p<0.004) or in those who reported at least three SCD complaints regarding their memory performance (SMC3) (HR=1.92 95% CI:1.05-3.52 p<0.035) at the baseline assessment. Subjective complaints regarding orientation were predictive of a greater hazard of frailty as defined by the Fried scale (HR=3.12 95% CI:1.45-6.73 p<0.004) and the Frailty Index (HR=3.59 95% CI:1.77-7.25 p<0.001).

CONCLUSION: Our findings demonstrate that healthy older adults who report SCD complaints regarding orientation or state that they have at least three memory complaints have a higher risk of developing frailty. Additionally, the number of participants with a clinical diagnosis of MCI or dementia, compared to individuals with normal aging, at follow-up was found to be significantly greater in cases with frailty according to both frailty definitions applied (p<0.001). Consequently, it is advisable to use screening questionnaires for SCD covering multiple cognitive domains in clinical practice for identifying and managing frailty, thus, implementing effective interventions to promote healthy aging.

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Key words: Mild cognitive impairment, dementia, healthy aging, older adults.

Introduction

Recent decades have witnessed an increased age shift in the worldwide population, subsequent to extended life expectancy (1). This increase in the number of older adults, which in 2018 surpassed the number of children, is expected to reach two billion globally in the next 30 years, with the majority being over 80 years old (2). It is commonly recognized that cognitive, physical, and mood status become increasingly vulnerable over the course of aging. This is associated with several adverse outcomes that affect the quality of life and increased prevalence of chronic diseases, such as dementia. As the population of the world ages, the ability to identify modifiable risk factors for cognitive decline and dementia, such as Subjective Cognitive Decline (SCD) and frailty in older adults, has become increasingly critical.

Subjective Cognitive Decline is the self-perception of cognitive decline or change, confusion, or memory loss, in the last 12 months compared to a previous normal cognitive status (3). The majority of individuals with SCD do not report implications for the most basic activities of daily living, and their independence is preserved. SCD has been associated with an increased risk of future cognitive decline and is one of the earliest noticeable symptoms of dementia (4). Cognitive decline, ranging from Mild Cognitive Impairment (MCI) to dementia, can have profound implications for an individual's overall health and well-being. A systematic review of sixteen studies showed that the conversion of individuals with SCD complaints to dementia or MCI was 1.5-3 times higher in older adults in relation to those who did not have subjective cognitive complaints (5). Another study reported that over the course of 5 years, 24.4% of individuals with SCD complaints will, have or are expected to convert to MCI, while 10.9% will progress to dementia, compared to 4.6% of those without SCD complaints (6).

Jessen and his colleagues set the framework for SCD, in the

absence of a widely accepted concept or a "gold standard", to overcome the difficulty of comparing studies with different definitions (5). SCD is a broad condition, associated with various factors, such as aging-related processes, underlying neurodegenerative diseases, psychiatric disorders, personality traits, and mood disorders (3).

Frailty is an age-related heterogeneous geriatric clinical syndrome associated with an increased risk for older adults to experience health problems, such as falls, hospitalization, increased risk of mortality, and reduced functioning (7). Although the consensus among experts is that frailty is a condition that entails the presence of a number of impairments, there is no single definition of frailty (8). Current definitions of frailty fall within two main categories: a) the phenotypic-physiologic approach and b) the multidomain approach, as part of a broader perspective (9). While these two operational definitions of frailty are the most widely used, there are many other variations (10). The first definition describes frailty as a distinct physiological process resulting from the dysregulation of multiple systems within the body. This definition of frailty derives from the work of Fried and colleagues and is most commonly used. Research has shown this definition to be consistent with that of a clinical syndrome (7). The multidomain definition utilizes the concept of an accumulation of deficits that incorporate 70 criteria, including physical and cognitive impairment, psychosocial risk factors, disability status, and chronic diseases that increase older adults' mortality (e.g., falls and delirium) (11). The estimated prevalence of frailty varies depending on the definition (12) used in population-based studies, from 4% to 22% (13, 14).

In the present longitudinal study, we explored the potential role of SCD complaints as an early sign of frailty. Both are independent risk factors for cognitive decline and dementia, appearing early in the course of the disease and have not been adequately investigated in relation to one another. The early identification of frailty is crucial, along with the implementation of preventive programs, which may slow decline, reduce the chance of adverse outcomes, and reduce healthcare costs (15).

Method

Participants

Participants were selected from the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD), as described previously (16). The HELIAD is a population-based, multidisciplinary-collaborative study designed to explore the epidemiology of subjective cognitive decline (SCD) and, the prevalence and incidence of mild cognitive impairment, Alzheimer's disease, and other types of dementia in the Greek population. Participants were 65 years of age and over and selected by random sampling of community-dwelling elderly individuals from the records of two Greek urban and rural populations.

The full cohort of the HELIAD consists of 1984 individuals who were randomly sampled and invited to participate in the study; thus, they can be considered representative of the whole elderly population in Greece. All participants were examined at baseline and then asked to attend a follow-up visit about 3 years after the initial evaluation. The baseline visits occurred between December 2009 and June 2016, while follow-up was conducted between January 2013 and July 2019. All participants provided informed consent before participation in the study. The institutional ethics review board of the University of Thessaly and the National and Kapodistrian University of Athens approved all procedures.

For the present study, the baseline sample consisted of 1,943 participants, (age: M=73.9, SD=5.45 years); of these, 1,121 individuals participated in the second evaluation. For the longitudinal analysis, we excluded participants with a diagnosis of frailty, MCI, dementia, severe anxiety, and depression on the first evaluation, and those with missing data on either assessment (n=146), resulting in a total sample of 975 participants in the follow-up, with an average follow-up interval of 3.1 years (SD=0.84 years) (Figure 3).

Evaluation – Procedure

Participants of the HELIAD underwent a structured clinical evaluation. In a face-to-face interview, participants provided information regarding (previous and current) medical problems, neurological conditions, neuropsychiatric symptoms, hospitalizations, surgeries, injuries, and current medications. In addition, an extensive structured physical examination, evaluating neurological signs and symptoms, was conducted for each participant. Structured questionnaires were administered to gather information about participants' functioning levels, social, mental, and physical activities, sleep, and dietary habits. Information regarding sociodemographic variables was also collected. All participants were also administered a comprehensive neuropsychological assessment of all major cognitive functions (16-18).

The interviews and assessments were conducted by qualified and licensed neurologists, neuropsychologists, and dietitians. For most of the participants, both evaluations were completed during a single visit, which lasted about 2-2.5 hours per participant. The health professionals were adequately trained on the study's protocol and procedures, to ensure the reliability and validity of the study's data.

Diagnosis of each participant's clinical and cognitive status emerged from regular diagnostic consensus meetings attended by all researchers. MCI was diagnosed when participants had subjective cognitive complaints and objective impairment in at least one cognitive domain, scoring at least 1.5 standard deviation (SD) below average, but preserved activities of daily living. More information regarding the diagnostic criteria and consensus procedures is described in detail elsewhere (16, 19). The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000) criteria.

Changes in the performance of daily activities and self-care habits were measured using the Blessed Dementia Scale. For the instrumental activities of daily living (IADLs), participants indicated whether they were able to perform eight IADLs

based on the Lawton–Brody scale, such as using a telephone, being responsible for their own medication, managing money, ability to use public or private transport, shopping, grooming, doing housework, and doing laundry. Socioeconomic status was divided into lower and higher categories, based on homeownership status (homeowner/renter), its area (m^2), and the number of rooms in the home. Ownership of cars or secondary residences as well as feasibility, length, and destination of summer vacations, was also taken into consideration. The data were adjusted for depressive symptoms over the past week, using the 15-item version of the Geriatric Depression Scale (GDS) and a cut-off score set at 6 points, and each item of the scale assessing the presence or absence of a specific depressive symptom (20, 21). Anxiety over the past week was measured using the 7-item anxiety subscale from the Hospital Anxiety and Depression scale (HADS-A). Each item is rated from 0 (best) to 3 (worst), and the cut-off score for anxiety was set at 8 points (22). A Greek version of the scale has been validated and has shown good psychometric properties (23).

Neuropsychological evaluation

Participants received a comprehensive neuropsychological assessment covering five cognitive domains: memory, language, attention/speed, executive functioning, and visual-spatial perception. Scores on each cognitive test were converted into z-scores using the mean and standard deviation (SD) values from the study sample. Subsequently, z-scores of individual neuropsychological tests were averaged to produce domain composite scores for the five cognitive domains mentioned above. The decision regarding the grouping of neuropsychological tests was based on prior knowledge of the cognitive functions that each test primarily reflects. Furthermore, neuropsychological domain composite scores were averaged to calculate a global composite neuropsychological functioning score. More information regarding the neuropsychological evaluation is described elsewhere (18, 24).

SCD Assessment

We assessed SCD based on eighteen self-reports of relevant complaints, through a series of single and selected questions taken from the medical history described in previously published articles (18, 24, 25). The questions assessing complaints regarding SCD were used as dichotomous variables based on the participant's responses. Each question had a possible rating of (0) "I do not have this complaint" or (1) "I have this complaint". We categorized each of the eighteen questions into four cognitive domains: memory, naming, orientation, and mathematical reasoning. The memory domain included questions that refer to robust memory complaints and had two subdomains: General Memory Decline (GMD) and Specific Memory Decline (SMD). The subcategory GMD included a gold standard set question «Have you had any memory problems lately?». The SMD included seven questions that referred to different memory tasks, i.e., remembering shopping lists, remembering things that happened recently, and a tendency to dwell on the past. Participants were characterized as having SCD if they gave a positive response to a single question in the GMD domain and/or at least one positive response to the seven questions of the SMD domain (SMD1) regarding memory. The other cognitive domains consisted of questions that do not solely refer to pure memory complaints. The domain regarding the decline in naming included two questions, in orientation five questions, and in mathematical reasoning three questions. Participants were characterized as having SCD if they gave at least one positive response to the specific domain's questions.

To examine SCD in depth, we created a variable that summarizes all positive responses in the four cognitive domains (memory, naming, orientation, and mathematical reasoning) in total with the abbreviation SAD (the sum of all domains with subjective cognitive decline). This variable was calculated as binary (0=no SCD complaints and 1=one or more SCD complaints in the aforementioned cognitive domains).

To examine any association between different categories of SCD and frailty, we performed statistical analyses by examining each cognitive domain of SCD separately with both frailty indices. For these analyses, we maintained the content of the naming, orientation, and mathematical reasoning domains, but created additional variables for the memory domain. The frequency analysis of the seven questions in this subdomain allowed us to redefine three variables using a broad, intermediate, and restrictive approach. The idea was to create a trichotomous variable to investigate the correlation of frailty in people with different levels of SCD burden concerning their memory ability. As the variable of at least one Specific Memory Decline (SMD1) (i.e., the participant gave at least one positive answer) was already in place, we used it as the variable that summarizes all SCD complaints. Additionally, we created the variable of at least two Specific complaints related to Memory Decline (SMD2) as well as that of at least three Specific complaints related to Memory Decline (SMD3), with the participants giving at least two and three positive answers, respectively, to the SMD questions of this category.

Frailty Assessment

We assessed frailty according to two different definitions that have been researched for efficacy, namely, a) Fried's definition (7) and b) the Frailty Index (FI) (26). These methods have also been described elsewhere (27, 28).

The Fried definition

This definition is most commonly accepted and belongs to the phenotypic approach derived from the work of Fried and colleagues (2001) in the Cardiovascular Health Study. Research has shown this definition to be consistent with that of clinical syndrome. It describes frailty as a distinct physiological process resulting from the dysregulation of multiple systems within the body. Participants who met three or more of the manifestations below were considered frail. The presence of

fewer than three criteria indicates prefrailty (7). Prefrailty is described as the state between frail and robust (non-frail) and indicates the dynamic nature of frailty: (a) Slow walking speed was defined as the lowest 20th percentile of our study population for the 4-minute walking speed test (adjusted for sex and height); (b) shrinking/weight loss was defined as body mass index (BMI) < 18.5 kg/m^2; (c) poor endurance/exhaustion was evaluated as a negative response to the question taken from the Geriatric Depression Scale "Do you feel full of energy?" (29); (d) low physical activity was estimated based on a validated questionnaire, the Athens Physical Activity Questionnaire (APAQ), which calculates participants' daily energy expenditure for physical activities (30). The lowest 20% for each sex was assumed to be indicative of frailty; (e) weakness was defined as grip strength in the lowest 20% adjusted for sex and BMI. The grip strength of the dominant hand was measured with an electronic dynamometer (Model MG-4800, the United Kingdom) and the mean strength of three trials was used in the current analysis.

The Frailty Index (FI)

The Frailty Index (FI) is used more frequently as a multidomain approach to assess frailty and is suggested by Rockwood and colleagues in the Canadian Study of Health and Aging (CSHA) (26). The FI is based on the routinely used Comprehensive Geriatric Assessment (CGA) and is based on 70 age-related multidomain deficits from a broader perspective, including mood, cognition, and incontinence. For the construction of FI, we followed the standard procedure described by Searle and colleagues (31). In the present study, 61 items regarding diseases, syndromes, functioning in activities of daily living, cognitive decline, mood disorders, and performance in physical activities were included for the assessment of frailty. The participants' deficit scores were totaled and according to this index, a score of 0.25 was determined as the frailty cut-off point (32). The higher the deficit score, the more advanced the frailty state.

Statistical analysis

Quantitative variables were expressed as mean values (SD), while qualitative variables were expressed as absolute and relative frequencies. For the comparisons of proportions, chi-squared and Fisher's exact tests were used. Student's t-tests were computed for the comparison of mean values between the two groups.

Univariate and multivariate Cox regression analyses were used to determine the association between the presence of SCD complaints (yes or no) at the baseline and having frailty at the second visit. The primary predictor was SCD complaints divided into four cognitive domains, and the outcome was the frailty status. Different categories of SCD complaints were examined with eight variables and frailty with two different methods, one, of the phenotypic-physiologic, and another of the multidomain approach. Irrespective of the definition used, frailty status was entered as a categorical variable (comparing frail to non-frail individuals). For the Fried approach, we included prefrail participants in the non-frail category. SCD complaints were entered into the models mentioned above, both as a continuous and a categorical variable.

We explored the role of various established risk factors of frailty using multivariate Cox regression analyses, in adjusted models. Specifically, the multivariate Cox regression analyses were conducted after adjusting for age, sex, educational level, socioeconomic status, comorbidity, global neuropsychological functioning score, and, the score of each participant on the depression and anxiety scales. Hazard ratios (HR) with 95% confidence intervals (95% CI) were computed from the results of the Cox regression analyses. Age, education (in years), comorbidity, global neuropsychological functioning score, and scores on the anxiety and depression scales were used as continuous variables, whereas sex was used as a dichotomous variable. Socioeconomic status (SES) was measured using four socioeconomic variables: economic reserves or assets, holiday/traveling, and leisure time activities. SES was used as a dichotomous variable with two levels «High» and «Low».

Kaplan–Meier survival estimates for frailty were graphed over the follow-up period. All reported p values are two-tailed. Statistical significance was set at $p<0.05$.and analyses were conducted using SPSS (version 23.0).

Results

Of the original sample of 1,984 older Greek individuals (≥65 years old), 1,121 remained in the longitudinal analysis. Participants diagnosed with frailty, Mild Cognitive Impairment (MCI), dementia, severe depression, and anxiety at baseline assessment were excluded from the analysis (n=146). The final sample consisted of 975 participants (399 men) with a mean age of 72.9 years (SD=5.4). The average follow-up interval was 3.1 years (SD=0.84 years). Sample characteristics at the baseline evaluation of the participants who had no frailty according to Fried's definition (n=937; sample B1) and for those that had no frailty according to the Frailty Index (n=842; sample B2) are presented in Table 1. The mean age was 72.8 years (SD=4.8) for sample B1 and 72.6 years (SD=4.9) for sample B2. The percentage of those with at least one comorbidity was 70.8% in sample B1 and 68.4% in sample B2. The characteristics of the two samples were similar except for depression scale scores, which were greater in sample B1 than in B2. The mean follow-up period was 3.1 years (SD=0.8 years), with a median of 3.0, ranging from 1.1 to 7.3 years. The proportion of individuals with frailty at follow-up, based on the presence of SCD complaints at the baseline assessment is shown in Table 2. According to Fried's definition at follow-up, a greater proportion of cases with frailty was found in those who had SCD complaints regarding orientation (OD) or at least three SCD complaints regarding memory (SMC3) at the baseline assessment. Also, according to the Frailty Index, the proportion of cases with frailty at follow-up was significantly greater in those who had SCD complaints about orientation at the baseline assessment.

Table 1. Sample characteristics at the baseline evaluation for the sample with no frailty according to Fried's definition (B1) and the Frailty Index (B2)

	Fried's definition N=937 B1	Frailty Index N=842 B2	
	M (%)	M (%)	p
Sex			
Men	370 (39.5)	346 (41.1)	0.491†
Women	567 (60.5)	496 (58.9)	
Education, mean (SD)	8.4 (4.9)	8.5 (4.9)	0.390¶
Age, mean (SD)	72.8 (4.8)	72.6 (4.9)	0.385¶
SES			
Lower	401 (42.8)	346 (41.1)	0.467†
Higher	536 (57.2)	496 (58.9)	
Smoking			
No	818 (88.9)	738 (88.9)	0.999†
Yes	102 (11.1)	92 (11.1)	
Drinking			
No	505 (54.8)	441 (53.0)	0.458†
Yes	417 (45.2)	391 (47.0)	
Hypertension			
No	329 (35.7)	317 (38.1)	0.295†
Yes	593 (64.3)	515 (61.9)	
Diabetes			
No	774 (84.1)	708 (85.3)	0.497†
Yes	146 (15.9)	122 (14.7)	
Coronary disease			
No	835 (90.8)	762 (91.7)	0.490†
Yes	85 (9.2)	69 (8.3)	
Stroke			
No	860 (93.3)	791 (95.1)	0.110†
Yes	62 (6.7)	41 (4.9)	
Comorbidity*			
No disease	267 (29.2)	261 (31.6)	0.273†
At least one disease	648 (70.8)	565 (68.4)	
HADS – Anxiety scale, mean (SD)	2.38 (3.6)	2.14 (3.5)	0.136¶
GDS – short form, mean (SD)	1.83 (3.0)	1.51 (2.7)	0.018¶
Global Neuropsychological Functioning score, mean (SD)	0.02 (0.7)	0.05 (0.7)	0.366¶

†Chi-square test; ¶Student's t-test; Abbreviation: SD, standard deviation; SES, socioeconomic status; HADS-A, Hospital Anxiety and Depression Scale - Anxiety Subscale; GDS, Geriatric Depression Scale; * Comorbidity refers to at least one of the following diseases: Hypertension, Diabetes, Stroke, or Coronary Heart Diseases

Concerning the sample with no frailty according to Fried's definition (B1), we found that those with SCD complaints regarding orientation had greater scores on the anxiety (p=0.004) and depression scale (p<0.001) than those without. For the B2 sample with no frailty according to the Frailty Index, we also found a greater score on the anxiety (p=0.020) and the depression scales (p=0.003) for those with SCD complaints regarding orientation. Furthermore, in the B2 sample, we found that a greater number of individuals with strokes were recorded among the cases that reported SCD complaints regarding orientation (18.5 vs. 5.9, p=0.03) at baseline assessment.

Univariate Cox regression analysis showed that participants with SCD complaints regarding orientation and those with at least three SCD complaints regarding memory at baseline assessment had a greater hazard for frailty at follow-up, as defined by Fried's approach (Table 3). The results were similar after adjusting the analysis for age, sex, educational level, socioeconomic factors, comorbidities, global

Table 2. The proportion of participants with and without frailty at follow-up according to the presence of SCD complaints at the baseline evaluation

	Fried's definition B1 sample N=937			Frailty Index B2 sample N=842		
	Without frailty	With frailty		Without frailty	With frailty	
	N (%)	N (%)	p	N (%)	N (%)	p
GMD						
No	589(92.2)	50(7.8)	0.813†	517(85.2)	90(14.8)	0.347†
Yes	276(92.6)	22(7.4)		194(82.6)	41(17.4)	
SMD1						
No	212(93.8)	14(6.2)	0.332†	186(84.9)	33(15.1)	0.816†
Yes	652(91.8)	58(8.2)		525(84.3)	98(15.7)	
SMD2						
No	600(92.9)	46(7.1)	0.327†	523(84.6)	95(15.4)	0.805†
Yes	264(91.0)	26(9.0)		188(83.9)	36(16.1)	
SMD3						
No	760(93.1)	56(6.9)	0.013†	645(84.9)	115(15.1)	0.298†
Yes	104(86.7)	16(13.3)		66(80.5)	16(19.5)	
ND						
No	626(92.7)	49(7.3)	0.415†	542(85.5)	92(14.5)	0.136†
Yes	237(91.2)	23(8.8)		168(81.2)	39(18.8)	
OD						
No	830(93.0)	62(7.0)	<0.001†	694(85.2)	121(14.8)	0.005¶
Yes	35(77.8)	10(22.2)		17(63.0)	10(37)	
CD						
No	851(92.4)	70(7.6)	0.466†	706(84.6)	129(15.4)	0.299¶
Yes	14(87.5)	2(12.5)		5(71.4)	2(28.6)	
SAD						
0	138(93.2)	10(6.8)	0.644†	124(84.4)	23(15.6)	>0.999†
1-3	727(92.1)	62(7.9)		587(84.5)	108(15.5)	

†Chi-square test; ¶Fisher's exact test; Abbreviation: SCD, subjective cognitive decline; GMD, general memory decline; SMD1, at least 1 specific complaint related to memory decline; SMD2, at least 2 specific complaints related to memory decline; SMD3, at least 3 specific complaints related to memory decline; ND, naming decline; OD, orientation decline; CD, calculation decline; SAD, the sum of all domains with subjective cognitive decline

neuropsychological functioning score, and scores on the anxiety and depression scales. Furthermore, both univariate and adjusted for age, sex, educational level, the existence of comorbidities, global neuropsychological functioning score and scores on the anxiety and depression scales. Cox regression analysis (Table 3) showed that participants with at least three memory complaints (SMD3) at baseline assessment and greater hazard of having frailty according to Fried's definition over time. Cox regression analyses also showed that participants with SCD complaints about orientation at the baseline assessment had a greater hazard of having frailty according to the Frailty Index at follow-up (Table 3). We found that SCD complaints regarding orientation were predictive of a greater hazard for frailty (Figures 1 and 2) based on both definitions.

Figure 1. Kaplan-Meier survival curves for frailty (using Fried's definition) according to SCD complaints regarding orientation

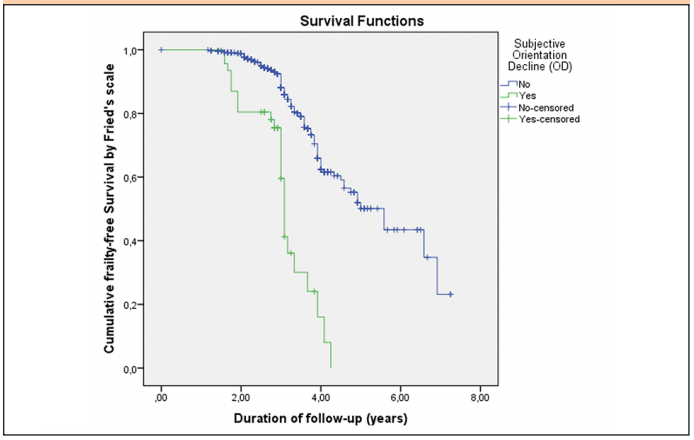
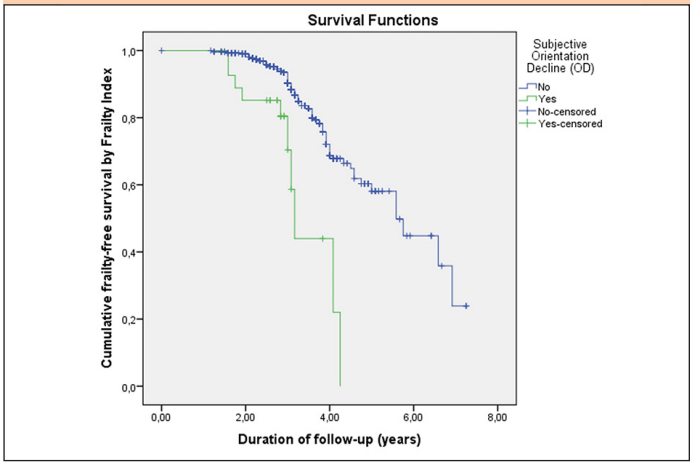


Figure 2. Kaplan-Meier survival curves for frailty (using the Frailty Index) according to SCD complaints regarding orientation



Concerning the total sample at follow-up, the proportion of participants who had a diagnosis of MCI was significantly greater in cases with frailty according to the Frailty Index (33.0% vs. 14.6%, p<0.001) and Fried's definition (28.9% vs. 17.8%, p<0.001). Additionally, the proportion of participants who had a diagnosis of dementia was significantly higher, in comparison to those with a diagnosis of MCI and normal aging, in cases with frailty according to the Frailty Index (20.5% vs. 3.3%, p<0.001) and Fried's definition (14.0% vs. 6.6%, p<0.001).

Discussion

In the present study, we investigated the predictive value of SCD on frailty for older adults in a longitudinal analysis of a population-based study. It is increasingly recognized that SCD is a clinical indicator of asymptomatic cognitive impairment and older adults with SCD have a higher probability of having MCI or dementia than those with normal cognition and without SCD complaints (33). The results of our study demonstrated that older adults with SCD complaints regarding orientation and with at least three memory complaints were more likely to develop frailty. We also found that exploring specific aspects of subjective memory decline is a better indicator than general questions (i.e., "Do you believe you forget?").

One prior study found associations between increased early frailty markers and increased SCD complaints, particularly for women, before the presence of objective cognitive impairment (34). Another study found the opposite, specifically, reporting a higher number of SCD complaints was associated with an increased likelihood of frailty (18). Both studies, however, had a cross-sectional design, whereas the present study is the first to examine longitudinal associations between SCD and frailty.

In the absence of a consensus definition, we examined frailty by using two different representative definitions, the phenotypic-physiologic, and the multidomain approach. It is generally accepted that the prevalence of frailty ranges from 4.0% to 59.1% depending on the assessment approach used to describe it (12). Studies measuring frailty according to the phenotypic approach, however, consistently report lower frailty prevalence than those utilizing the multidomain definitions. This is also the case in the present study, which found the smallest prevalence using Fried's definition (7.7%) and the highest with the Frailty Index (15.5%). These results are quite similar to those reported by Theou and colleagues (35). This 7.8-point difference in the prevalence of frailty may be explained by the fact that the Frailty Index is based on the routinely used multidimensional geriatric assessment, or as it is also called, the Comprehensive Geriatric Assessment (CGA) (36), and involves a broad range of indices, including mood, cognition, and incontinence, whereas Fried's definition is based on objective measurements.

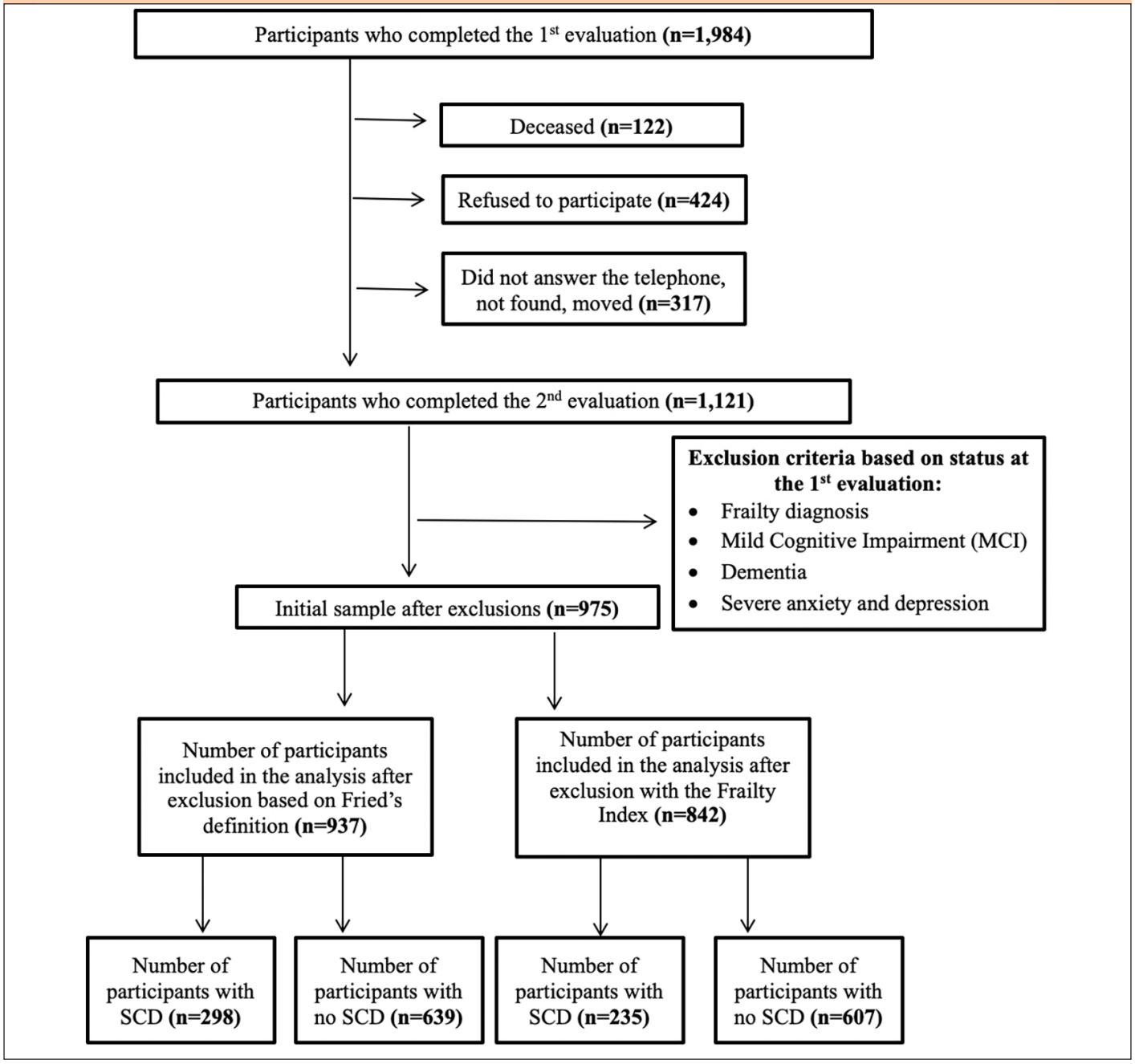
In the absence of a standardized approach to assessing SCD, in the present study we employed two definitions for optimal assessment. It is unclear whether specific aspects of SCD may be differentially related to frailty. In our study, we

Table 3. Results from Cox regression analyses with the two frailty approaches, Fried's definition and the Frailty Index, as dependent variables

	Fried's scale				Frailty Index			
	HR (95% CI) Univariate¶	p	HR (95% CI) Adjusted †	p	HR (95% CI) Univariate¶	p	HR (95% CI) Adjusted†	p
GMD	0.81 (0.49-1.33)	0.400	0.92 (0.52-1.61)	0.763	0.95 (0.66-1.38)	0.783	1.13 (0.76-1.67)	0.556
SMD1	1.60 (0.89-2.88)	0.116	0.85 (0.45-1.62)	0.622	1.34 (0.90- 2.00)	0.146	0.84 (0.55-1.29)	0.430
SMD2	1.20 (0.74-1.93)	0.468	0.80 (0.45-1.42)	0.449	0.96 (0.65-1.41)	0.826	0.79 (0.52-1.21)	0.277
SMD3	1.98 (1.13-3.47)	0.017	1.92 (1.05-3.52)	0.035	1.12 (0.67-1.90)	0.662	1.18 (0.66-2.10)	0.574
ND	1.19 (0.72-1.96)	0.490	1.36 (0.80-2.32)	0.266	1.19 (0.82-1.73)	0.372	1.40 (0.95-2.07)	0.093
OD	4.60 (2.34-9.06)	<0.001	3.12 (1.45-6.73)	0.004	3.91 (2.04-7.49)	<0.001	3.59 (1.77-7.25)	<0.001
CD SAD	1.65 (0.40-6.75)	0.486	0.89 (0.20-3.93)	0.878	1.32 (0.33-5.33)	0.701	0.73 (0.09-5.49)	0.758
1-3 vs. 0	1.27 (0.65-2.48)	0.493	0.80 (0.38-1.66)	0.542	1.11 (0.71-1.75)	0.648	0.76 (0.48-1.22)	0.259

¶Hazard Ratio (95% Confidence Interval); †Adjusted for age, sex, educational level, comorbidity scale, neuropsychological functioning score, and scores on the HADS-Anxiety scale and the GDS depression short scale; Abbreviation: SCD, subjective cognitive decline; GMD, general memory decline; SMD1, at least 1 specific complaint related to memory decline; SMD2, at least 2 specific complaints related to memory decline; SMD3, at least 3 specific complaints related to memory decline; ND, naming decline; OD, orientation decline; CD, calculation decline; SAD, the sum of all domains with subjective cognitive decline

Figure 3. Flow chart of the study sample in the HELIAD longitudinal study related to the present analyses



examined SCD at baseline with a series of eighteen questions taken from each person's medical history. The questions regarding SCD were categorized according to the cognitive domain, and we also created a variable that summarizes all positive responses. During the follow-up assessment, a greater proportion of cases with frailty was found in those who had SCD complaints regarding orientation, or at least three SCD complaints regarding memory at the baseline evaluation, according to Fried's definition than those with no complaints. Also, according to the Frailty Index, the proportion of cases with frailty at follow-up was significantly greater in those who had SCD complaints regarding orientation at the baseline assessment. Overall, these results suggest the need to explore specific aspects of SCD, covering all major cognitive domains, as this is a more sensitive measure than a general question (i.e., "Do you believe you forget?").

The association between SCD and frailty may be elucidated by potential neurobiological factors, as well as the aging processes, including underlying cognitive decline and neurodegenerative disorders. Previous longitudinal studies have found an association between SCD and frailty, with an increased risk of future cognitive decline and progression to MCI and dementia (37). According to the literature, there is evidence that SCD complaints occur at a preclinical stage and are associated with subclinical asymptomatic neurodegeneration (38). The number of participants in the present study with a diagnosis of MCI or dementia at follow-up was greater in cases with frailty according to both definitions used ($p<0.001$),

relative to those without frailty. This finding is consistent with previous studies showing that frailty is a risk factor for dementia (39). Therefore, we speculated that there must be a common pathway to determine these two conditions among older adults (specifically, subjective cognitive decline and frailty) and suggest the need for further investigation into the biological mechanism underlying this linkage.

There are some limitations that must be considered when interpreting our results. First, in our attempt to operationalize frailty with two representative scales of the phenotypic-physiologic and the multidomain approach, we modified some of the definitions used. The modified operationalization of Fried's definition may be considered a limitation. We believe, however, that although some parameters were measured using different scales than those originally proposed by Fried and colleagues, we remained close to the recommended criteria. The prevalence rate found in the present sample is similar to that reported in other studies using the same definition [40]. In an epidemiological study, such as HELIAD, a significant proportion of the clinical data are self-reported, thus their reliability may be subject to bias. Moreover, the fact that some definitions use objective measures, whereas others use subjective measures of participants' performance may explain the variability in findings related to the frailty syndrome.

On the other hand, our study has several strengths. We conducted a community-based prospective cohort study to examine SCD and frailty, thus we were able to establish a cause–outcome association. The large sample, the standardized methods used in the HELIAD study, and the large amount of information collected for each participant enabled the use of different concept definitions for optimal assessment of SCD and frailty. In the absence of broadly accepted questionnaires, this is one of the major strengths of the present study. Moreover, our study was based on face-to-face interviews that were conducted by certified neurologists, neuropsychologists, and dieticians. This may have augmented the accuracy of our measurements of all criteria used in the SCD and frailty definitions. In addition, we performed a comprehensive clinical and neuropsychological evaluation, and participants' diagnoses were based on consensus meetings of the investigators and experimenters, with the use of standard criteria; we also adjusted the analyses for potential confounders.

In conclusion, the present findings revealed a significant association between SCD and frailty in older adults. SCD was positively associated with frailty, even after adjusting for potential confounding factors. Our results indicated that further investigation of the complex mechanisms between SCD and frailty is important. Subjective Cognitive Decline is a growing public health issue and Periodic Comprehensive Geriatric Assessment (CGA), including the evaluation of SCD complaints, and multimodal interventions adjusted to potential frailty status, are necessary to provide the best interventions for older adults. A key step in this direction is to create standardized screening tools for both SCD and frailty. Finally, encouraging systematic usage of these subjective self-reports regarding cognition and early identification of frail individuals would be of significant benefit as frailty is a dynamic syndrome that may be preventable (41). Encouraging older adults and health care professionals to discuss and/or administer questionnaires for the evaluation and early detection of modifiable risk factors like SCD, during routine medical check-ups, may help alleviate the future impact of SCD, and prevent possible progression to frailty, and cognitive decline, and dementia that would be an additional burden on the health and wellness of the individuals and the public health systems. The present study may set the criteria for investigating the association of SCD and frailty while forming a clinical and research framework for creating a questionnaire for the early and accurate detection of SCD. The completion of a third evaluation in the context of HELIAD, as well as laboratory and imaging data, may aid in confirming the causal hypotheses outlined in the present paper and elucidate the mechanisms by which SCD is associated with frailty.

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