The association between physical frailty and cognitive performance in older adults aged 60-96 years. Data from the “Good Aging in Skåne” (GÅS) Swedish population study.

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Abstract

Background: The association between physical frailty and performance in different cognitive domains in the absence of cognitive disorders is poorly understood. Hence, we aimed to explore the associations between frailty levels based on the Fried Physical Frailty Phenotype and performance of different cognitive domains. We also aimed to examine the associations between cognitive function and each criterion in the Fried Frailty Scale using the same cognitive domains in a non-dementia population aged 60–96 years.

Methods: This cross-sectional study included 4,329 participants aged 60–93 years, drawn from the “Good Aging in Skåne” population study. Frailty indices included handgrip strength, physical endurance, body mass index (BMI), physical activity, and walking speed. Cognitive function was assessed across eight domains: episodic memory, processing speed, semantic memory, verbal fluency, working memory, attention, executive function, and visual perception. We constructed adjusted multiple linear regression models for each cognitive domain, with the frailty levels as the independent variable. Likewise, we constructed linear regression models with each cognitive domain as the dependent variable and frailty criteria as independent variables.

Results: Physical frailty was associated with poor performance in episodic memory, processing speed, semantic memory, verbal fluency, working memory, attention, and executive functions (p < 0.001 for all associations). Weaker hand grip strength was independently associated with poorer performance in all cognitive domains (p < 0.001–0.015).

Conclusions: Higher levels of frailty were associated with poorer performance in all cognitive domains except visual perception. Describing frailty by considering cognitive functioning may provide a better understanding of frailty.
Keywords: cognition, frailty, older adults.

Introduction

Frailty is a physical state of decreased resistance to stressors that commonly occurs in older populations. The prevalence of frailty in community-dwelling populations ranges from 4.0% to 59.1%, with an increase in incidence closely associated with advancing age [1]; however, frailty should not be viewed as a part of normal aging [2]. Frail individuals are vulnerable to both individual and environmental stressors, are more easily affected by adverse health outcomes than their non-frail counterparts [3, 4], and have higher risks of institutionalization, hospitalization, and premature mortality [5]. Although frailty is characterized by impaired physical abilities such as a less active lifestyle, low endurance, slow walking, and reduced muscle strength [5], whether cognitive status should be included to better describe the concept of frailty remains unknown [6, 7].

Physical frailty is associated with increased risks of Alzheimer’s disease and vascular dementia [8]. Even in populations without dementia, frailty leads to lower global cognitive performance [9-12]. In a systematic review of 36 studies, frailty was found to have the largest impact on processing speed, followed by executive function, attention, and working memory [13]. However, the reported associations between performance in specific cognitive domains and frailty are inconsistent [9, 10,14].

The concept of cognitive frailty was first proposed in 2013 by a consensus group of researchers from the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) to describe the presence of both physical frailty and cognitive impairment [15].

Frailty is also associated with a greater decline in cognitive performance over time, both globally and in specific cognitive functions of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability [14, 16]. Frail and cognitively impaired individuals experience increased vulnerability over four years, with a higher
incidence of disability [17]. Thus, a subpopulation of frail older adults is at greater risk of adverse health outcomes.

Most studies on the relationship between physical frailty and cognition have used global measures such as the mini-mental state examination (MMSE) [18] and the Montreal cognitive assessment (MoCA) [19]. However, the association between frailty and cognitive function based on a larger number of cognitive domains has been examined rarely, and to our knowledge, no specific recognized patterns of cognitive function associated with levels of frailty have been reported. Hence, the present study primarily aimed to explore and present updated information on the associations between frailty levels and performance in eight cognitive domains—episodic memory, processing speed, semantic memory, verbal fluency, working memory, attention, executive function, and visual perception,—using the MMSE as a global measure, which can provide a deeper understanding of frailty. The secondary aim was to investigate the associations between each criterion in the frailty index and functionalities of each cognitive domain. We adjusted these associations for age, sex, marital status, educational level, cerebrovascular disease, and sedative drug use.

Materials and Methods

Participants

The participants in this cross-sectional study were drawn from the “Good Aging in Skåne” (GÅS) longitudinal population study, which has been ongoing since 2001 and is part of the Swedish National Aging and Care (SNAC) survey [20]. The design of the GÅS study is described elsewhere [21, 22]. Eligible informants randomized from the national population register were invited to participate in the study by letter, and informed consent was obtained. The present study included a total of 5,804 (63.5%) eligible informants aged 60–93 years living in the province of Skåne, the southernmost part of Sweden, representing both rural and urban areas. The exclusion criteria were current Alzheimer’s disease; cerebrovascular or frontal lobe
dementia diagnosis (n = 127); MMSE score < 18 points (n = 37); depressed mood (>7 points on
the Montgomery–Åsberg depression rating scale [MADRS]) (n = 74); Parkinson’s disease
(n = 39); language difficulties, i.e., did not understand or speak Swedish (n = 44); no results
from any cognitive tests (n = 503), and insufficient data to assess frailty owing to consultation
by home visits offered to the most vulnerable group, which meant that no walking speed tests or
hand grip tests could be performed (n = 651). Finally, the study sample consisted of 4,329
participants (2,042 [47.2%] men and 2,287 [52.8%] women) (Table 1).

The participants underwent comprehensive and standardized physiological,
psychological, and medical assessments. Self-reported questionnaires were used to obtain data
on sociodemographic factors and lifestyle habits. The examinations were performed at the
research clinic or the participants’ homes for those with impaired health. Qualified physicians
and psychologists conducted all medical examinations and psychological tests.

Frailty assessments
Frailty levels were assessed using the Fried Physical Frailty Phenotype [5]. Frailty was defined
as the presence of three or more of the following five criteria: weakness, low physical
endurance, low body mass index (BMI) (an alternative to weight loss of 4.5 kg in the previous
year), low physical activity level, and slow walking [5]. We defined participants who fulfilled
one or two criteria as pre-frail, whereas those who did not fulfill any criteria present were
classified as non-frail.

Weakness was assessed by handgrip strength using a Grippit®, a validated electronic
device for measuring handgrip force [24]. The standardized testing procedure included the
participants in a sitting position and instructions on how to squeeze the grip [25]. The data of
best performance among those tested for both hands after two repeated measurements were
included in the analysis. After stratification by sex and BMI, we defined weakness as the
quintile with the lowest measured value [5].
Physical endurance was assessed using the following two questions: 1. “In recent weeks, how much of the time have you felt full of energy?,” with possible responses of “None of the time,” “Most of the time,” and “All the time” and 2. “Do you feel tired and sleep more than 2 hours during the day?” with possible responses of “Yes” and “No” [26]. We categorized participants who answered “None of the time” to the first question or “Yes” to the second as having low physical endurance. We calculated BMI as weight (kg)/height squared (m²) and defined values ≤20.0 kg/m² as low BMI [27, 28].

Physical activity was assessed using the question, “How much do you exercise or make a physical effort during your spare time or in your home?”. The responses included mostly sedentary (sedentary or only light housework), light activity (2–4 hours per week of ordinary housework and shopping), and strenuous activity (1–3 hours per week of gymnastics or sports) [25]. We categorized participants who reported mostly sedentary or only light housework as having a low level of physical activity.

Walking speed was measured based on the time required to travel 15 m at a normal (comfortable) speed [25]. The test was conducted in a hospital corridor, and the participants were allowed to accelerate and decelerate several meters before and after the test. The time required to walk 15 m was recorded using a digital stopwatch. After stratifying by sex and mean height, we defined slow walking as that with the speed of the slowest quintile [5].

Cognitive function assessments
The cognitive test battery included 13 cognitive tests (Table 2) representing eight cognitive domains: episodic memory, processing speed, semantic memory, verbal fluency, working memory, attention, executive function, and visual perception, with the MMSE as a global measure of cognitive ability [29].

Episodic memory was assessed based on “free recall” and “recognition” [30]. In free recall, the participants were shown 16 unrelated words, each for 5 s. They were then asked to
recall as many words as possible. One point was given for each correctly memorized word, with a maximum score of 16. In the “recognition” test, the same 16 words were mixed with 16 new words, and the participants were asked to identify which of the 32 words were presented earlier. The score was calculated based on the number of correctly recognized words subtracted from the number of incorrectly recognized words, with a maximum score of 16 points [31].

Processing speed was assessed based on “comparing figures” and “digit cancellation” [32, 33]. Comparing figures consisted of pairs of figures, some of which were identical, whereas others were not. One point was awarded for each correct assessment with a maximum score of 30 [32]. Digit cancellation was based on the identification of a specific number from a continuum of rows of different numbers. The participants were instructed to mark every occurrence of the number four. One point was awarded for each correctly identified row with a maximum score of 43 points.

Semantic memory was assessed using the SRBI synonym test [34], in which participants were presented with 30 different words and instructed to identify synonymous words among five alternatives. The outcome was measured as the number of correctly selected synonyms, with a maximum score of 30.

Verbal fluency was assessed using four tests. Semantic fluency was tested by asking the participant to verbally list as many words as possible related to animals and professions in one minute. Phonemic fluency was tested by asking the participant to mention words beginning with the letters F and A [35]. The mean number of words produced was the outcome of these four tests.

Working memory was assessed using the “digit span forward” and “digit span backward” tests [36]. In the digit span forward test, the participant was instructed to repeat a sequence of numbers ranging from two to eight after the test leader. In the digit span backward test, the participants were asked to repeat the same numbers in reverse order. The outcome was
measured by the number of correctly repeated sequences, with a maximum score of seven points per test.

Attention was assessed using trail making tests A (TMT-A) and B (TMT-B) [35]. In TMT-A, the participants were instructed to draw a line between 13 numbers in ascending order as quickly as possible [37], with no time limit for completing the test. The outcome of the TMT-A was the time taken in seconds to complete the 12 correct connections.

Executive function was assessed using a modified version of the trail making test B (TMT-B) [35] [29]. The participants were instructed to draw a line between seven numbers and six letters in alternating numerical and alphabetical order as quickly as possible, with no time limit for completing the tests. The outcome of the TMT-B was the time required in seconds to complete the 12 correct connections. Participants who did not complete the test correctly were excluded.

Visual perception was assessed using “mental rotations” [38]. The participants were assigned ten different tasks involving three-dimensional cubes and were instructed to identify one correctly rotated cube from among three options. The outcome of this test was the number of correct answers divided by the number of completed tasks, with scores ranging from 0 to 10.

Global cognitive status was assessed using the MMSE, with a scale score ranging from 0 to 30 points. We defined cognitive impairment when the score was ≤24 points [18].

Medical history and socio-demographics

A previous diagnosis of ischemic stroke, transient ischemic attack (TIA), reversible ischemic neurological deficit (RIND), or cerebral hemorrhage was used to identify a history of cerebrovascular disease. We verified the reported diseases using the National Diagnosis Registry and medical records after obtaining permission from the participants.

We divided education into elementary school, high school, or college level.
We dichotomized marital status as living alone or living with someone in a permanent relationship.

The use of sedatives included drugs classified under headings N01 to N07 in the Anatomical Therapeutic Chemical System; that is, anesthetics, analgesics, antiepileptics, psycholeptics (sedatives, hypnotics), psychoanaleptics (antidepressants), and parasympathomimetics [39].

**Ethics approval and consent to participate**

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the regional ethics committee of Lund University 2010-2012, registration no. LU 744-00. All participants provided written informed consent and allowed their information to be retrieved from the National Patient Register records. The participants were informed that they could withdraw from the study at any time.

**Statistical analysis**

The descriptive statistics of the study sample, including frailty levels, are presented in Table 1. We tested the differences in the proportions of frail, pre-frail, and non-frail older adults according to sex, marital status, education, medication, and cerebrovascular disease using the chi-squared ($\chi^2$) test. Kruskal–Wallis test was used to compare the variations in the proportions of frail, pre-frail, and non-frail individuals in relation to the non-normally distributed variable of age (Table 1).

The cognitive test data were normally distributed with skewness and kurtosis +/- 2, except for TMT-A and B. Owing to unequal variance in the results of the cognitive tests comparing frail, pre-frail, and non-frail older adults, we tested the differences in means using Welch's analysis of variance (Table 2) [40].
To enable a comparison of the cognitive test results, we used the formula $Z = y_i - m/SD$, where $y_i$ is the individual score, $m$ is the test mean, and SD is the standard deviation, which was applied before calculating the total cognitive performance score. We used the mean Z-score for domains that included more than one cognitive test and used Z-scores in all linear regression models.

We constructed two sets of linear regression models. First, after controlling for age, sex, education, cerebrovascular disease, marital status, and use of sedatives, each domain-specific cognitive function was the dependent variable, and the levels of frailty were the independent variables (Table 3). Second, each specific cognitive domain served as the dependent variable, with dichotomized frailty criteria as independent variables, which were likewise controlled for age, sex, education, marital status, use of sedatives, and cerebrovascular disease. All frailty criteria and covariates were simultaneously entered into the model (Table 4).

All regression models were tested for multicollinearity and none had a variance inflation factor $> 1.5$ [41]. The residuals were normally distributed, with skewness within $+/- 2$ and a kurtosis within $+/- 7$ [42].

We set statistical significance at $p < 0.05$ and conducted all statistical analyses using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

**Results**

The study sample consisted of 4,329 participants (mean age 68.3 years (SD = 9.6), 52.8% women). The prevalences of pre-frailty and frailty were 45.3% and 9.7%, respectively. Within the pre-frail group, 67.6 % (n =1,318) fulfilled one criterion, while 32.4% (n = 633) fulfilled two criteria. Within the frail group, 70.8% (n =296) fulfilled three criteria, 26.8 % (n =112) fulfilled four criteria, and 2.4% (n=10) fulfilled five criteria. Frailty was associated with older age, lower educational level, sedative use, and cerebrovascular disease (Table 1). In this study, 24% of participants aged $\geq 80$ years were frail compared with 4% of those aged 60–69 years.
The most common frailty criterion in the study population was physical endurance (34.8%), followed by walking speed (19.1%), handgrip strength (18.8%), physical activity (15.7%), and low BMI (3.4%) (Table 1). Underweight was identified in 3.0% (n = 85), 3.7% (n = 18), and 4.3% (n = 44) of participants in age groups 60–69, 70–79, and ≥80 years, respectively.

Frail and pre-frail participants scored significantly lower than non-frail participants in all cognitive tests, as did pre-frail than frail participants (Table 2).

The results of the fully adjusted linear regression models showed that frailty was significantly associated with cognitive performance in all domains, except visual perception, while the difference between non-frailty and frailty was not significant (p = 0.053) (Table 3). Apart from the MMSE as a global cognitive measure, the three domains most strongly associated with being frail were processing speed (B = -0.40, Sd 95% = -0.49/-0.32, p < 0.001), verbal fluency (B = -0.40, Sd 95% = -0.48/-0.32, p < 0.001), and attention (B = 0.43, Sd 95% = 0.35/0.51, p < 0.001) (Table 3).

Testing the independent association between each frailty criterion and cognitive domains showed that hand grip strength was associated with all domains, while low BMI was not associated with any domain except processing speed. Physical endurance was associated with episodic memory, processing speed, verbal fluency, working memory, attention, executive function, and MMSE. Physical activity was associated with episodic memory, processing speed, semantic memory, verbal fluency, and working memory, whereas walking speed was associated with episodic memory, processing speed, verbal fluency, attention, and executive function. BMI and walking speed were not associated with MMSE (B = 0.06, Sd 95% = -0.10/0.21, p = 0.468) and (B = -0.07, Sd 95% = -0.15/-0.02, p = 0.113) (Table 4).

As shown in Table 2, the cognitive tests had missing data ranging from 1.9% (digit cancellation) to 15.35% (Trail Making Test B). Attrition was unevenly distributed among frailty groups. The non-frail group had the least attrition, whereas the frail group showed the highest attrition. The main explanations for uneven attrition between the frail groups were related to age
differences and differences in education, where those in the highest age decade (≥80 years) and those with lower education showed higher attrition rates (Table 2).

**Discussion**

The findings of this cross-sectional study revealed significant differences between the non-frail and pre-frail/frail groups as well as between the pre-frail and frail groups in all cognitive tests (Table 2). On comparing levels of frailty and composite scores in the cognitive domains of episodic memory, processing speed, word fluency, and global cognition (the MMSE), physical frailty was associated with impaired cognitive abilities. As both functional ability and cognition deteriorate with increasing age and more than half of the frail group were ≥80 years of age, this result is reasonable, even when impaired functional ability or cognition appear separately [43]. However, these results contradict those of earlier studies reporting no difference in episodic memory, working memory, and global cognition [6] or delayed memory and verbal fluency [44] between non-frail and frail older adults. However, our results are consistent with those of previous studies reporting lower performance in global cognition [9, 10, 11, 45, 46], executive function, memory (episodic memory), attention [11], digit backward (working memory), verbal fluency, and visual-spatial function (visual perception) [46]. The results of the latter test did not differ significantly between non-frail and frail older adults (p = 0.053), possibly because we excluded participants with severe visual impairment; that is, milder visual impairment may have had a greater effect on the results of this test.

The differences in cognitive performance between frailty levels were small but still significant. These minor differences can be partially explained by the fact that we did not include individuals with dementia or depression. Another possible explanation is the homogeneity among those classified as frail. As mentioned above, we observed a lack of representation at the severe end of the frailty spectrum, indicating possible attrition of the frailest older adults.
The reported associations between frailty and specific cognitive functions indicate that processing speed is the most affected by a higher level of frailty, followed by executive function, attention, and working memory [14]. Although the processing speed, attention, and verbal fluency domains showed the strongest association with frailty in the present study, the differences between them were only minor, making it difficult to determine whether any domain was more closely related to the frailty phenotype. These results may indicate that at the time of the study, frailty was associated with deterioration in all cognitive domains, suggesting that cognitive status, including as many cognitive tests as possible, should be considered when assessing frailty. From a clinical perspective, the results suggest that healthcare professionals should consider screening older adults for cognitive impairment when assessing frailty, as this could facilitate intervention and lead to the earlier detection of frailty, which in turn can lead to better-adapted care and potentially prevent frailty worsening.

In the adjusted analyses examining the association between each of the frailty criteria and cognitive domains, hand grip strength, physical endurance, physical activity, and walking speed were independently associated with five or more of the eight cognitive domains, whereas low BMI was only associated with processing speed. These results are partially consistent with those of previous studies that linked handgrip strength, walking speed [47, 48, 49], physical activity [50], and physical endurance [6] with cognitive functioning. The non-significant associations between frailty criteria and cognitive domains and MMSE scores found in this study were mainly explained by the adjustment for education, especially university studies.

However, the few longitudinal studies on frailty and cognition have reported inconsistent results. Frailty is associated with a steeper decline in cognition over time in both general and specific cognitive functions [12, 13]. In another study, poorer baseline performance was observed during cognitive tests among those classified as frail but whether cognitive functioning over time is further aggravated by frailty was not established [47]. The limited comparability and differences in the results between studies can perhaps be explained by the
different study approaches. Thus, research methodology must be standardized, particularly in terms of frailty criteria and cognitive testing.

Although many frail older adults are undernourished, the non-significant association between low BMI and cognitive ability found in the present study might be explained by the incorrect estimation of BMI owing to inaccurate height, resulting in an underestimation of participants with a low BMI. Height reduces because of physiological changes that occur with aging, primarily due to axial compression of the spinal column and muscle-to-fat conversion; therefore, calculating height based on a more stable measure such as knee height may yield a more accurate BMI [51]. However, although the proportion of malnourished older adults would have been slightly higher, this would not completely explain the lack of association between low BMI and cognitive ability. A more plausible explanation is that frailty is not confined to individuals with low BMI. Obesity is also associated with frailty [52, 53], suggesting a U-shaped relationship between frailty and BMI [54]. Although beyond the scope of this study, a post-hoc analysis revealed that within the non-frail group, 0.1% were underweight and 16.2% were obese (>30 kg/m²), whereas the corresponding proportions within the frail group were 11.5% and 24.2%, respectively; i.e., both low weight and obesity were more common in the frail group. The use of BMI as a substitute for weight loss requires further discussion. A further question is whether the relationship between BMI and cognitive ability, shown for the entire study population (Table 4), remained in the group aged ≥80 years, which had the largest proportion of underweight individuals. The result remained; that is, the group aged ≥80 years showed no significant relationships between being underweight and cognitive test results. For example, we observed no significant association between being underweight and MMSE score in the adjusted model (B = -0.08, Sd 95% = -0.40/0.23, p = 0.623). This result is consistent with that of a previous study reporting that being underweight, overweight, or obese, compared to normal weight, was not associated with impaired cognitive ability [55].
Two comprehensive concepts that should be considered when discussing frailty and cognition are comorbidities and activities of daily living (ADL). While the participants could be acceptably classified based on their frailty levels, we could rule out the possibility that some participants were restricted in terms of ADL or were affected by a disease, which may have influenced the results. In the case of people who are diseased, in addition to the exclusion of dementia, adjustments were made for cerebrovascular disease; that is, diseases that may have affected the outcome of the cognitive tests. In the case of ADL, participants who were dependent on personal activities of daily living (PADL) were significantly overrepresented among those classified as frail, as 12.8% were dependent in at least one of the following activities: bathing, dressing, toileting, mobility, and food intake, compared with pre-frail (1.7%) and robust (0.1%) participants (data not shown). However, participants with frailty showed no significant difference in MMSE scores between those who were dependent and independent in ADL. Thus, although we did not include ADL status and morbidity, except for cerebrovascular disease, in the analyses, this probably would not have affected the results of the cognitive tests.

Another question is whether the place of residence is associated with the prevalence of frailty. Frailty is more common in rural areas, which is partly explained by limited educational resources and accessibility of healthcare services [56]. However, the results of the present study did not show that frailty was related to urban or rural living. The prevalence of frailty was slightly higher in urban areas (9.7%) than in rural areas (9.4%) (Table 1). The contributing reasons for this contrary finding may be that education is roughly equivalent in the entire region of Skåne where this study was conducted, and healthcare is of a high standard and includes both primary care through contact with a general practitioner and highly specialized hospital care [57].

Contrary to previous reports, the results of the cognitive tests did not differ significantly between urban and rural areas [58]. For example, the mean MMSE scores for
participants living in urban and non-urban areas were 27.3 points (SD = 2.2) and 27.4 points (SD = 2.1), respectively (p = 0.383).

Limitations
Owing to the cross-sectional study design, we could not determine whether some cognitive domains were affected earlier than others, nor could we establish the speed of reduced cognitive ability or whether physical frailty precedes a deterioration in cognitive ability or vice versa. In addition to the fact that we are unable to identify any direct causal connections, cognitive performance also showed intrapersonal variance in both healthy and cognitively impaired populations. This variance is better considered in longitudinal study designs, in which a general trend can become visible over time.

We could not control for factors, including smoking and alcohol habits, nutrition, physical activity, social participation, inflammation caused by trauma, hormonal changes [59], and stress [60], that can also negatively affect cognitive ability.

To reduce selection bias, home visits were offered to participants with disabilities or those who had difficulty traveling to the research clinic for other reasons. Nevertheless, selection bias cannot be ruled out, as the cognitive tests were intended for participants without severe vision or hearing loss. Another limitation was that walking speed and handgrip strength (part of the Fried Physical Frailty Phenotype) could not be tested during home visits. This probably contributed to the over-representation of frail older adults among those who were excluded.

Strengths
This study has several strengths. First, the large study sample is representative of the general population of older adults living in both rural and urban areas. Second, the examinations were conducted by professionally certified personnel specially trained in various test situations.
Finally, as many different variants of the cognitive tests in this study are in use, we presented all the tests to facilitate comparisons with previous surveys.

**Conclusion**

Within an older general population without dementia, non-frail, pre-frail, and frail individuals showed significant deterioration in cognitive function in the domains of episodic memory, processing speed, semantic memory, verbal fluency, working memory, attention, executive functioning, and visual perception when compared with Fried Physical Frailty Phenotypes adjusted for age, sex, marital status, education, cerebrovascular disease, and sedative drug use. Frailty was prevalent in older age groups and was noted in one of four participants aged >80 years. These findings illustrate the concurrent loss of physical and cognitive function in older adults. Describing frailty not only based on physical ability but also by including simultaneous shortcomings in cognitive functioning may provide a better understanding of frailty. Together with the knowledge that frailty can be reversed [61], these findings suggest the potential for the development of new treatment strategies for this vulnerable group. Furthermore, health professionals should consider screening older adults for cognitive impairment when assessing frailty to facilitate interventions and allow earlier frailty diagnosis.

**Acknowledgments**

**Conflicts of interests**

The researchers claim no conflicts of interest.

**Funding**

Financial disclosure: The Good Aging in Skåne project, a part of the Swedish National Study on Ageing and Care (www.snac.org), is supported by the Swedish Ministry of Health and Social
Affairs, county Region Skåne, Medical Faculty at Lund University, Swedish Research Council (grant 2017-01613), Konung Gustaf V och Drottning Viktoria Frimurarestiftelse, and Gyllenstiernska Krapperupstiftelsen.

Authors’ contributions

Conceptualization, HE and KL. Data curation, SE, HE, and KL. Funding acquisition, SE. Investigation, KL, HE, SE, and L S-W. Methodology, KL, HE, SE, and L S-W. Writing-original draft, KL, HE, SE, and L S-W. Writing-review and editing, KL, HE, SE, and L S-W. All authors read and approved the final manuscript.