Original Study

Physical Frailty and Cognitive Functioning in Depressed Older Adults: Findings From the NESDO Study

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Keywords:
Physical frailty
Cognitive functioning
Cognitive frailty
Late-life depression

Abstract

Objectives: Cognitive frailty has recently been defined as the co-occurrence of physical frailty and cognitive impairment. Late-life depression is associated with both physical frailty and cognitive impairment, especially processing speed and executive functioning. The objective of this study was to investigate the association between physical frailty and cognitive functioning in depressed older persons.

Design: Baseline data of a depressed cohort, participating in the Netherlands Study of Depression in Older persons (NESDO).

Setting: Primary care and specialized mental health care.

Participants: A total of 378 patients (>60 years) with depression according to DSM-IV criteria and a MMSE score of 24 points or higher.

Measurements: The physical frailty phenotype as well as its individual criteria (weight loss, weakness, exhaustion, slowness, low activity). Cognitive functioning was examined in 4 domains: verbal memory, working memory, interference control, and processing speed.

Results: Of the 378 depressed patients (range 60–90 years; 66.1% women), 61 were classified as robust (no frailty criteria present), 214 as prefrail (1 or 2 frailty criteria present), and 103 as frail (>3 criteria). Linear regression analyses, adjusted for confounders, showed that the severity of physical frailty was associated with poorer verbal memory (ß = -0.13, P = .039), slower processing speed (ß = -0.20, P = .001), and decreased working memory (ß = -0.18, P = .004), but not with changes in interference control (ß = 0.04, P = .54).

Conclusion: In late-life depression, physical frailty is associated with poorer cognitive functioning, although not consistently for executive functioning. Future studies should examine whether cognitive impairment in the presence of physical frailty belongs to cognitive frailty and is indeed an important concept to identify a specific subgroup of depressed older patients, who need multimodal treatment strategies integrating physical, cognitive, and psychological functioning.

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Postponing age-related diseases and disability is of eminent importance for maintaining a person’s independence, including independent living and social participation, as well as to minimize the ancillary economic and societal burden. Medical communities focus on detection of prodromal states and high-risk conditions aimed to interfere as early as possible to delay or even prevent impairment. This focus has culminated in the concept of physical frailty. A consensus paper defined physical frailty as a medical syndrome that reflects a critical decrease of the functional and physiological reserves of...
multiple organic systems. This state of vulnerability has been associated with adverse health outcomes, including chronic course of depression, disability, hospitalization, and mortality.\textsuperscript{2,4} Conventionally, the concept of physical frailty primarily concentrated on the physical domain.\textsuperscript{4} Recently a consensus panel argued that cognitive impairment is not only associated with physical frailty, but also shares many pathophysiological mechanisms with physical frailty. To stimulate research in this field, the concept “cognitive frailty” was proposed, emphasizing the important role of brain aging.\textsuperscript{3} Cognitive frailty was defined as the presence of cognitive deficits in physically frail older persons without dementia.\textsuperscript{3} This subtype of frailty is deemed important, as it may represent a prodromal phase for neurodegenerative diseases and is potentially a suitable target for early intervention.\textsuperscript{4} Unfortunately, the consensus paper does not define cognitive impairment, neither with respect to the severity of impairment, nor with respect to the cognitive domains affected.

The association between physical frailty and cognitive impairment is complex. Some researchers consider the concept of cognitive frailty as a distinctive medical syndrome on its own,\textsuperscript{5,6} which can be examined prospectively in relation to physical frailty. A systematic review has identified 11 longitudinal studies that show the predictive value of physical frailty for subsequent cognitive decline or dementia.\textsuperscript{7} Although less often studied, cognitive impairment conversely may be a risk factor of physical frailty.\textsuperscript{8} In line with the consensus paper on cognitive frailty,\textsuperscript{3} some researchers have included cognitive impairment as a component of physical frailty for 2 reasons. First, adding cognitive impairment to a frailty index adds to its predictive validity for adverse health outcomes.\textsuperscript{9} Second, significant overlap exists in the mechanisms underlying physical frailty and cognitive impairment.\textsuperscript{10}

Late-life depression is associated with both physical frailty\textsuperscript{11} and cognitive impairment.\textsuperscript{12} Whereas cognitive impairment in depression has been considered temporarily due to motivational and attentional problems, recent articles stress the persistence of cognitive deficits after remission of depressive symptoms.\textsuperscript{13} To our knowledge, the association between physical frailty and cognitive impairment has not been studied among clinically depressed older patients. This is important, as depression itself is also a risk factor of many age-related diseases.\textsuperscript{14–16} The importance of depression and/or psychological components within the concept of cognitive frailty has been mentioned briefly in the consensus statement on cognitive frailty, but was not further elaborated on because of the lack of empirical data.\textsuperscript{4}

The present study examines the association between physical frailty and cognition in a large sample of depressed older persons taking 4 cognitive domains into account. We hypothesize that in depressed older persons physical frailty is associated with poor functioning in all cognitive domains examined.

**Methods**

**Study Sample**

Data from the Netherlands Study of Depression in Older persons (NESDO) were used.\textsuperscript{17} NESDO is a multisite prospective cohort study, including 378 depressed and 132 nondepressed older persons (60–93 years). For this specific study, only the 378 depressed older persons were included. Recruitment of depressed older persons was from both mental health care institutes (86.2%) and general practices (13.8%) so as to include persons with late-life depression in various developmental and severity stages. The prevalence of frailty did not differ across the different echelons of our health care system.\textsuperscript{11} Depressed persons were included when they fulfilled the DSM-IV criteria for major depression (95.0%), dysthymia (26.5%), or minor depression (5.0%). These numbers do not add to exactly 100% because of cases with double depression (ie, a major depressive episode on a dysthmic disorder). Exclusion criteria of the NESDO study were a clinical diagnosis (or suspicion by an old age psychiatrist) of dementia, psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder; a Mini-Mental State Examination score (MMSE) below 18 (of 30 points); and insufficient command of the Dutch language. In NESDO, the cutoff on the MMSE was chosen low to be able to include also the most severely depressed patients. Data collection of the baseline measurement started in 2007 and was finished in 2010. The population and methods of the NESDO study have been described in detail elsewhere.\textsuperscript{17} The study was approved by the ethical boards of the participating institutes and written informed consent was obtained from all participants.

**Measurements**

**Psychopathology**

Diagnoses of major depression and dysthymia were assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization version 2.1; lifetime version) according to DSM-IV-R criteria. The CIDI is a structured clinical interview and has high validity for depressive and anxiety disorders.\textsuperscript{18} Questions were added to determine the DSM-IV research diagnosis of current minor depression. The severity of depressive symptoms was assessed with the self-report version of the Inventory of Depressive Symptomatology (IDS).\textsuperscript{19} Antidepressant drug use in the previous week was determined by inspection of the medication containers and classified according to the Anatomical Therapeutic Chemical (ATC) classification. The use of selective serotonin reuptake inhibitors (SSRIs) (ATC-code: N06AB), tricyclic antidepressants (TCAs) (ATC-code: N06AA), and other anti-depressants (ATC-code: N06AX, N06AF, N06AG) was dichotomized into yes/no. Use of benzodiazepines (ATC codes: N03AE, N05BA, N05CD, N05CF) for more than 50% of the time was considered as present, and this variable was dichotomized into yes/no.

**Cognitive functioning**

With 3 cognitive tasks, cognitive function was assessed: (1) the short version of the Stroop Color-Word test,\textsuperscript{20,21} (2) the subtest Digit Span (both forward and backward) from the Wechsler Adult Intelligence Scale (WAIS) Scale,\textsuperscript{22} and (3) a modified version of the Auditory Verbal Learning Test.\textsuperscript{23}

- During the first 2 tasks of the Stroop Color-Word test, participants had to read the words blue, green, yellow, or red (task I) or color of rectangles (task II) aloud as fast and accurate as possible. During Stroop task III, participants were shown a card with 4 lines of names of the 4 different colors, printed in an incongruent ink color. This time, participants were asked to read the color of the ink of the printed word aloud as fast and accurately as possible.
- During the Digit Span of the WAIS, participants were asked to repeat a series of digits recited by the research assistant. After every correct series, a longer series of digits was presented, adding 1 digit each time. The Digit Span forward score was defined as the longest series of digits a participant could repeat. The Digit Span backward was the longest series of digits a participant could repeat in the reverse order.
- During the modified Auditory Verbal Learning Test, a research assistant read aloud 10 common nouns. Immediately after this, participants were asked to recall as many words as possible. This was done 5 times in immediate succession. After a delay of 15 to 25 minutes during which other (unrelated) questions were asked, the interviewers asked the respondents to recall the words again. The delayed recall score consisted of the total number of correctly recalled words after the delay.

From these 3 cognitive tasks, 4 cognitive domain scores were created by means of factor analyses.\textsuperscript{12} For all 4 domains, higher
scores represent better cognitive functioning. The first domain, verbal memory, comprised the delayed recall task of a modified version of the Rey Auditory Verbal Learning Test. The second domain, processing speed, comprised the total number of seconds to complete the Stroop I and Stroop II tests. This variable was transformed by taking the multiplicative inverse (ie, 1/x) to make it normally distributed, and make higher scores represent better scores. The third domain, cognitive flexibility, comprised the interference score from the Stroop test. The Stroop interference score is computed with the formula: \((t_{III} - 0.5 \times (t_{II} + t_{III}))/0.5 \times (t_{II} + t_{III}) \times 100\%\). This variable was transformed by taking the natural logarithm to make it normally distributed and multiplied by –1 so higher scores represent better scores. The fourth cognitive domain comprised attention: times the number of minutes performing the activity per week), and obesity with the BMI.

Physical frailty
Physical frailty was assessed according to the criteria of Fried et al., including weight loss, weakness, poor endurance and energy, slowness, and low physical activity level. A person is classified as frail when 3 or more criteria are present, prefrail when 1 or 2 criteria are present, and robust in case none of the criteria are present.

- Unintentional weight loss was defined as a positive response on the CIDI question about unwanted weight loss of a minimum of 1 kg a week, during 2 or more consecutive weeks or a body mass index (BMI) of less than 18.5 kg/m².
- A handgrip dynamometer was used to assess weakness. Participants were asked to perform 2 squeezes with the dynamometer, in standing position, using their dominant hand. The best performance, recorded as strength in kilograms, was used for analysis. Cutoff scores were stratified by gender and BMI quartiles according to Fried and colleagues.
- Exhaustion (poor endurance and energy) was determined by 2 questions from the Center for Epidemiological Studies-Depression scale (CES-D), similar to other studies. “I felt that everything I did was an effort” and “I could not get going.” Both items were scored on a 4-point scale (0 through 3). Participants answering 2 or 3 to either of these 2 items were categorized as positive for this frailty item.
- Slowness was measured by a 6-meter walking test. For men with a height of 173 cm or less, the cutoff time was 9 seconds. For men taller than 173 cm the cutoff time was 8 seconds. The cutoff time on this criterion for women with a height of 159 cm or less was 9 seconds, for women taller than 159 cm the cutoff time was 8 seconds (extrapolated from the data of Fried and colleagues).
- Low physical activity level was defined as no daily activities such as walking and gardening, or the performance of sports less than once weekly. The self-administered version of the International Physical Activities Questionnaire (IPAQ) was used to collect physical activity data over the past 7 days.

Because the 2 performance-based components (ie, gait speed [GS] and handgrip strength [HGS]) had to be dichotomized for calculating the sum score of the Fried Frailty Index (FFI), we included both variables also as a continuous measure when analyzing the association between frailty components and cognition. Because GS has a skewed distribution, this variable was normalized by a log-transformation after having trimmed 3 outliers at the mean value plus 3 SDs. HGS also had a skewed distribution and became normally distributed after log-transformation.

Covariates
Variables known to be related with both cognitive performance and late-life depression are age, level of education, sex, alcohol use, smoking status, obesity, physical activity, and chronic diseases. Therefore, these variables were included as confounders. In the baseline assessment, detailed information about age, sex, and number of years of education was collected. Alcohol use was assessed with the Alcohol Use Disorder Identification Test (AUDIT), a self-reported questionnaire. Smoking status was dichotomized into “smoker” (current smoker) and “nonsmoker” (never smoked and former smoker). Physical activity (measured with the IPAQ) in MET-minutes (ratio of energy expenditure during activity compared with rest, times the number of minutes performing the activity per week), and obesity with the BMI.

The number of chronic diseases was assessed by self-report questions about the presence of somatic diseases (cardiac diseases, cerebrovascular accident, hypertension, peripheral atherosclerosis, diabetes mellitus, chronic nonspecific lung disease, liver diseases, thyroid diseases, epilepsy, intestinal diseases, arthritis/arthritis, and cancer) (www.CBS.nl). The accuracy of self-reporting of these chronic diseases was shown to be adequate and independent of decline in cognitive functioning in comparison with data received from general practitioners. Finally, to control for depression severity level and medication effects, we also included the IDS sum score as well as psychotropic drug use (antidepressants and benzodiazepines) as covariates.

Statistical Analyses
First, basic characteristics of the study sample were presented, stratified by frailty status (ie, robust, prefrail, and frail). Robust, prefrail, and frail depressed older patients were compared with each other using the \(\chi^2\) test (categorical variables) and Student t test (continuous variables).

Subsequently, associations were tested by different linear regression models with cognitive performance (each of the 4 domains tested in separate models) as the dependent variable and frailty as the independent variable. The relationship between physical frailty and cognitive performance was examined for several indices of physical frailty: (1) the sum score of 5 dichotomized FFI criteria (scale 0–5), (2) the presence of each criterion of the FFI (weight loss, weakness, poor endurance and energy, slowness, and low physical activity level) as the dichotomized variable, and finally (3) GS and HGS as continuous variables.

We present both unadjusted results as well as fully adjusted models adjusted for age, sex, level of education, severity of depressive symptoms, number of chronic diseases including hypertension, use of alcohol (AUDIT sum score), smoking (yes/no), BMI, level of physical activity (MET-minutes a week), SSRI use (yes/no), TCA use (yes/no), other antidepressant drug use (yes/no), and benzodiazepine drug use (yes/no).

Because the present study focuses on cognitive frailty (ie, cognitive impairment no dementia among frail persons), we ran a sensitivity analyses excluding patients with an MMSE score below the traditional cutoff of 24 points (n = 14).

Results
Of the 378 depressed older persons, 103 (27.2%) were physically frail. Table 1 shows the characteristics of the robust, prefrail, and frail patients separately.

Table 2 shows associations between physical frailty according to sum score of the FFI and for each criterion as the binary variable and cognitive performance. The sum score of the FFI is significantly associated with verbal memory, processing speed, and working memory. Of the specific criteria, weight loss is only significantly associated with working memory, whereas weakness was significantly associated with verbal memory and processing speed. Exhaustion was not...
significantly associated with cognitive performance. Slowness showed significant associations with processing speed and working memory. Low activity presented only a significant association with verbal memory. Of the cognitive performances, interference control was not significantly associated with the sum score of the FFI nor with any of the 5 criteria as binary variables.

In Table 3, associations between GS and HGS, both as continuous variables and cognitive performance are shown. In the fully adjusted models, GS is significantly associated with verbal memory, processing speed, and working memory, whereas HGS is significantly associated with verbal memory, processing speed, and interference control.

Finally, all analyses were repeated excluding patients with a MMSE score below 24 points (n = 14). The main findings did not change substantially (see Appendices 1, 2, and 3 for detailed information).

### Discussion

Within this large cohort of clinically depressed older persons, we found that physical frailty is associated with worse cognitive performance in the domains of verbal memory, processing speed, and working memory. These associations were independent of depression severity and primarily driven by the components of muscle weakness, slowness, and low activity level. These findings extend to findings...
from previous studies conducted in community-dwelling older persons. A recent case-control study comparing frail and nonfrail older persons showed a robust association between the level of daily functioning task in our study, however, was not associated with physical frailty and different domains of cognition. A small case-control study comparing frail and nonfrail older persons showed that this might be due to a lack of statistical power in some studies. As late-life depression is consistently identified as a risk factor for dementia and Alzheimer disease, our sample may be considered as a high-risk sample for memory impairment.

Potential Pathways and the Importance of Depression

Although several studies have reported that physical frailty and impaired cognitive functioning are related, currently there are no causal links found yet. Potential mechanisms that may underlie both physical frailty and cognitive impairment include neuropathological changes, hormonal changes, vascular damage, chronic inflammation, nutritional factors, vitamin D deficiency, and increased insulin resistance. The extent by which similar mechanisms affect physical frailty and cognition, however, may be different. For example, the annual rate of decline in cognitive functioning and worsening of frailty was highly correlated over 6 years ($r = -0.73, P < .001$). Among the deceased group ($n = 848$), neuropathological changes explained 9% of worsening of physical frailty and 30% of worsening cognition.

Depression also seems to be an important condition to take into account when disentangling the interaction between physical frailty and cognitive impairment. Several studies have demonstrated that late-life depression can have a detrimental effect on cognition. Late-life depression has also been associated with an age-related loss of muscle mass and muscle strength, referred to as sarcopenia, suggesting that older adults with depressive symptoms may be at risk for physical frailty. The prevalence of physical frailty is indeed increased in late-life depression, independent of comorbid chronic somatic diseases and disability. Because late-life depression and physical frailty also share some of their etiological pathways, depression might be a driving force for further deterioration of cognition in physically frail persons. This may eventually lead to development of a vicious circle resulting in cognitive deterioration. To better understand the common underlying pathophysiological mechanisms between physical frailty and neuropsychiatric disorders, the inclusion of cognition in the operationalization of the concept physical frailty may be important.

Methodological Considerations

To our knowledge, this is the first study in which the relationship between physical frailty and cognitive functioning in a sample of depressed older adults was investigated. Moreover, we included a large number of participants diagnosed with depression formally according to DSM-IV criteria and fully adjusted for potentially confounding psychotropic drug use. However, for proper interpretation, some limitations also should be acknowledged. First, because of the cross-sectional design of this study, it was not possible to demonstrate causal relationships between physical frailty and cognition. Second,
we applied a cutoff on the MMSE of 18 points so as to include also the most severely depressed patients. Nonetheless, we included only patients who were considered depressed by an old age psychiatrist without suspicion for dementia, and only included if a diagnosis of depression was confirmed by the CIDI. Moreover, a sensitivity analysis excluding all patients with a MMSE score less than 24 points revealed similar results (see Appendices). Third, lack of motivation, eventually caused by depression, could have negatively affected the physical frailty measurements.

Conclusion

Within our population of depressed older persons, physical frailty is associated with poorer cognitive functioning. Co-occurrence of physical frailty and cognitive impairment may contribute to the negative health effects associated with late-life depression. The concept of cognitive frailty as a subtype of frailty in depressed older persons may contribute to the development of multimodal treatment strategies, focusing on cognitive, psychological, and physical domains. More knowledge of the potential interactions among these domains and their clinical consequences, as well as with their pathophysiological pathway, seems important when improving mental health care and quality of life in older persons.

References

## Appendix

### Appendix 1

**Population Characteristics, Stratified by Presence of the Physical Frailty Phenotype (Sensitivity Analyses Excluding Patients With an MMSE Score Below the Traditional Cutoff of 24 Points)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Robust Persons</th>
<th>Prefrail Persons</th>
<th>Frail Persons</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 60</td>
<td>n = 210</td>
<td>n = 94</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>68.3 (6.4)</td>
<td>70.0 (7.0)</td>
<td>73.7 (8.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>44 (73.3)</td>
<td>132 (62.9)</td>
<td>64 (68.1)</td>
<td>.281</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>11.1 (3.5)</td>
<td>10.6 (3.5)</td>
<td>9.5 (3.0)</td>
<td>.009</td>
</tr>
<tr>
<td><strong>Lifestyle:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>13 (21.7)</td>
<td>60 (28.6)</td>
<td>24 (26.1)</td>
<td>.558</td>
</tr>
<tr>
<td>Physical activity (MET-minutes/wk), mean (SD)</td>
<td>4064 (2959)</td>
<td>2591 (2356)</td>
<td>947 (1371)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.7 (3.7)</td>
<td>26.2 (4.3)</td>
<td>27.2 (5.1)</td>
<td>.076</td>
</tr>
<tr>
<td>Alcohol usage (AUDIT), mean (SD)</td>
<td>3.3 (3.7)</td>
<td>2.7 (3.6)</td>
<td>2.1 (3.1)</td>
<td>.148</td>
</tr>
<tr>
<td><strong>Clinical characteristics:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of depression (IDS), mean (SD)</td>
<td>22.9 (10.9)</td>
<td>28.6 (12.1)</td>
<td>37.0 (12.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of chronic diseases, mean (SD)</td>
<td>1.6 (1.2)</td>
<td>2.0 (1.4)</td>
<td>2.5 (1.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Use of antidepressants:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI, n (%)</td>
<td>15 (25.0)</td>
<td>57 (27.3)</td>
<td>28 (29.8)</td>
<td>.803</td>
</tr>
<tr>
<td>TCA, n (%)</td>
<td>10 (16.7)</td>
<td>45 (21.5)</td>
<td>22 (23.4)</td>
<td>.599</td>
</tr>
<tr>
<td>Other antidepressant, n (%)</td>
<td>16 (26.7)</td>
<td>55 (26.2)</td>
<td>33 (35.5)</td>
<td>.239</td>
</tr>
<tr>
<td>Benzodiazepines, n (%)</td>
<td>14 (23.3)</td>
<td>81 (38.6)</td>
<td>46 (48.9)</td>
<td>.006</td>
</tr>
<tr>
<td><strong>Cognitive functioning:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global cognitive functioning (MMSE), mean (SD)</td>
<td>28.1 (1.5)</td>
<td>28.0 (1.6)</td>
<td>27.6 (1.8)</td>
<td>.087</td>
</tr>
<tr>
<td>Verbal memory, mean (SD)</td>
<td>6.6 (1.9)</td>
<td>6.0 (2.1)</td>
<td>5.2 (2.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Processing speed, mean (SD)</td>
<td>0.0472 (0.0081)</td>
<td>0.0455 (0.0080)</td>
<td>0.0400 (0.0093)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Interference control, mean (SD)</td>
<td>−0.255 (0.483)</td>
<td>−0.193 (0.536)</td>
<td>−0.311 (0.594)</td>
<td>.226</td>
</tr>
<tr>
<td>Working memory, mean (SD)</td>
<td>13.9 (3.0)</td>
<td>13.4 (3.2)</td>
<td>12.6 (3.1)</td>
<td>.021</td>
</tr>
</tbody>
</table>

*Based on 1-way analysis of variance in case of continuous variables and χ^2 tests in case of dichotomous variables.

### Appendix 2

**Association Between Frailty According to the FFI (Sum Score) and Presence of Each Criterion of the FFI (Present or Not) and Different Measures of Cognitive Functioning (Dependent Variables) (Sensitivity Analyses Excluding Patients With an MMSE Score Below the Traditional Cutoff of 24 Points)**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Frailty (FFI)</th>
<th>Verbal Memory</th>
<th>Processing Speed</th>
<th>Interference Control</th>
<th>Working Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Weight loss</td>
<td>Unadjusted</td>
<td>−0.24</td>
<td>-.31</td>
<td>−0.07</td>
<td>−0.23</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted*</td>
<td>−0.13</td>
<td>-.21</td>
<td>0.04</td>
<td>−0.18</td>
</tr>
<tr>
<td>2: Weakness</td>
<td>Unadjusted</td>
<td>−0.02</td>
<td>0.02</td>
<td>−0.02</td>
<td>−0.11</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted*</td>
<td>0.01</td>
<td>.04</td>
<td>−0.02</td>
<td>−0.08</td>
</tr>
<tr>
<td>3: Exhaustion</td>
<td>Unadjusted</td>
<td>−0.21</td>
<td>−0.25</td>
<td>−0.10</td>
<td>−0.18</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted*</td>
<td>−0.12</td>
<td>−0.13</td>
<td>−0.05</td>
<td>−0.07</td>
</tr>
<tr>
<td>4: Slowness</td>
<td>Unadjusted</td>
<td>−0.06</td>
<td>−0.07</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted*</td>
<td>&lt; -0.01</td>
<td>0.01</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>5: Low activity</td>
<td>Unadjusted</td>
<td>−0.15</td>
<td>−0.3</td>
<td>−0.09</td>
<td>−0.24</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted*</td>
<td>−0.05</td>
<td>−0.28</td>
<td>0.01</td>
<td>−0.20</td>
</tr>
</tbody>
</table>

*β*, completely standardized regression coefficient.

*Adjusted for age, sex, level of education, and severity of depressive symptoms; number of chronic diseases including hypertension; use of alcohol (AUDIT sum score); smoking (yes/no); BMI, level of physical activity (MET-minutes a week); SSRI use (yes/no); TCA use (yes/no); other antidepressant drug use (yes/no), and benzodiazepine drug use (yes/no).

1Not corrected for BMI (as BMI was included in the operationalization of this criterion).
2Not corrected for physical activity (as the IPAQ questionnaire was used to operationalize this criterion).
Appendix 3
Association Between GS (Dimensional) and HGS (Dimensional) With Different Measures of Cognitive Functioning (Dependent Variables) (Sensitivity Analyses Excluding Patients With an MMSE Score Below the Traditional Cutoff of 24 Points)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Verbal Memory</th>
<th>Processing Speed</th>
<th>Interference Control</th>
<th>Working Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>-0.21</td>
<td>&lt;.001</td>
<td>-0.46</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>-0.11</td>
<td>.088</td>
<td>-0.37</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HGS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.14</td>
<td>.007</td>
<td>0.28</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>0.14</td>
<td>.042</td>
<td>0.16</td>
<td>.022</td>
</tr>
</tbody>
</table>

\( \beta \), completely standardized regression coefficient.

*Adjusted for age, sex, level of education, and severity of depressive symptoms; number of chronic diseases including hypertension; use of alcohol (AUDIT sum score); smoking (yes/no); BMI; level of physical activity (MET-minutes a week); SSRI use (yes/no); TCA use (yes/no); other antidepressant drug use (yes/no); and benzodiazepine drug use (yes/no).