Physical Frailty Correlates With Behavioral and Psychological Symptoms of Dementia and Caregiver Burden in Alzheimer's Disease

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ABSTRACT

Objective: The aim of this study was to clarify the association of physical frailty with behavioral and psychological symptoms of dementia (BPSD) and caregiver burden in patients with Alzheimer's disease (AD).

Methods: The subjects were 1,193 AD patients who presented to the Memory Clinic at the National Center for Geriatrics and Gerontology of Japan during the period from October 2010 to February 2015 (mean ± SD age = 78.8 ± 6.3 years; female, 68.6%). AD was diagnosed based on the criteria of the National Institute on Aging and Alzheimer's Association workgroups. The Frailty Index (FI) was calculated as the ratio of actual to 38 potential deficits. BPSD and caregiver burden were assessed by using the Dementia Behavior Disturbance Scale (DBD) and the Japanese version of Zarit Burden Interview (J-ZBI). Multiple linear regression analyses and structural equation modeling (SEM) were performed to examine the relationship between the FI, DBD, and J-ZBI.

Results: The subjects' mean FI score was 0.16 ± 0.10, with 663 (55.6%) and 198 (16.6%) subjects shown to be pre-frail ($0.08 \le FI < 0.25$) and frail ($FI \ge 0.25$), respectively. Multiple linear regression analyses and SEM showed that the FI was independently associated with both DBD ($\beta = 0.30$, $P < .001$) and J-ZBI ($\beta = 0.13$, $P < .001$). Moreover, when the FI was considered as a categorical variable, even pre-frailty was associated with increased DBD score ($\beta = 0.16$, $P < .001$) and J-ZBI score ($\beta = 0.09$, $P = .003$).

Conclusions: The presence of not only physical frailty but also pre-frailty, as determined by the FI, could increase BPSD and caregiver burden in patients with AD.

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Alzheimer's disease (AD) is a growing health issue and is the most common type of dementia. In addition to cognitive deficits and progressive deterioration in functional performance, AD is characterized by several behavioral and psychological symptoms of dementia (BPSD), with more than 80% of patients with dementia shown to experience at least 1 neuropsychiatric symptom.[1] In the AD process that can be either mild cognitive impairment or dementia, BPSD are seen across all stages of AD.[1] The presence of BPSD not only has been linked to more rapid cognitive and functional decline, hospitalization, and institutionalization[1–4] but also is shown to be strongly associated with caregiver burden in AD.[5,6]

Although the mechanism of BPSD has not been fully clarified, several previous studies have revealed a range of risk factors for BPSD: patient sociodemographic factors (older age,[7–11] sex,[8,9] less education,[7,9,10] and marital status[9]); disease-related factors (severity of disease,[7–10,12] impairments of activities of daily living [ADL],[9,11] disease duration,[7] and the presence of the apolipoprotein E [*APOE*] ε4 allele[8,10]); and health-related factors (general medical health,[8,11] comorbidities,[10,12] and malnutrition[13,14]). Our previous studies[15,16] demonstrated that these health-related factors were more prevalent among AD patients than among those with normal cognitive function and increased with cognitive decline.

In this context, frailty has received attention in relation to impaired cognitive function and dementia. Frailty is characterized by increased vulnerability to stressors caused by a cumulative decline in multiple physiological systems, which results in an increased risk of adverse health outcomes.[17] To date, there are 2 widely used operational definitions of frailty: (1) the frailty phenotype proposed by Fried et al[18] in the Cardiovascular Health Study and (2) the Frailty Index (FI) proposed by Rockwood et al[19] in the Canadian Study of Health and Aging. Based on the concept that frailty is a pre-disability syndrome, the frailty phenotype clearly differentiates between frailty and disability. Thus, the use of the frailty phenotype is preferred as a screening tool for frailty in the first estimation.[20] Conversely, based on the concept that frailty results from the accumulation of deficits, the FI takes into account impairments of ADL, comorbidities, and geriatric syndromes and can be generated after a comprehensive geriatric assessment.[19] A conspicuous feature of the FI is that it can be applied in all

Clinical Points

- Many studies have demonstrated a significant association of physical frailty with dementia, but the impact of frailty on behavioral and psychiatric symptoms of dementia (BPSD) or caregiver burden has been unknown.
- As identified by the cumulative deficit model, not only frailty but also pre-frailty could increase BPSD and caregiver burden.
- Comprehensive health assessment and intervention are required to adequately address BPSD and caregiver burden.

elderly individuals, including those with dementia or those already experiencing disability.[20] In actuality, the FI has the capacity to predict the risk of negative health outcomes, such as hospitalization, institutionalization, and mortality, in nursing home residents and patients with dementia, as well as community-dwelling elderly individuals.[17,21–23]

Recently, Kelaiditi et al[22] showed that the FI significantly predicted mortality and hospitalization in AD patients. Moreover, they[24] demonstrated after 1 year of follow-up that the FI was significantly associated with cognitive decline in patients with mild-to-moderate AD. These previous studies indicate that frailty accounts primarily for heterogeneity in AD, such as cognitive decline and prognosis, independently of the AD pathology.

To date, no studies have examined the association between the FI, BPSD, and caregiver burden. In the present study, therefore, we aimed to examine the effect of deficits on BPSD and caregiver burden in patients with AD. Moreover, in order to test the hypothesis that deficits have both direct and indirect effects (mediated through increased BPSD) on caregiver burden (Supplementary Figure 1), structural equation modeling (SEM) was employed. Establishing the association between the FI, BPSD, and caregiver burden could provide a basis for successful strategies for reducing BPSD and caregiver burden.

METHODS

Subjects

The study subjects comprised outpatients 60 years or older who presented to the Memory Clinic at the National Center for Geriatrics and Gerontology (NCGG) of Japan during the period from October 2010 to February 2015. We included a total of 1,578 subjects who had been clinically diagnosed with probable or possible AD based on the criteria of the National Institute on Aging and Alzheimer's Association workgroups.[25] Of these, 385 subjects who could not complete a comprehensive geriatric assessment were excluded. Finally, we included 1,193 patients for analysis. The Ethics Committee of the NCGG approved the study protocol. The purpose, nature, and potential risks of the study were fully explained to the subjects, and all subjects gave written informed consent before participating in the study.

Frailty Index

The FI was generated based on a standard procedure.[26] The FI included 38 deficits, and these variables were assessed by caregivers by using a questionnaire about patients' basic and instrumental ADL, comorbidities, and geriatric syndromes. Each deficit was dichotomized to the interval 0–1, where values of 0 and 1 were assumed to indicate the absence and presence of the deficit, respectively. All the deficits used to generate the FI as well as their prevalence are shown in Supplementary Table 1. The FI score was calculated for each individual as the ratio of actual to potential deficits (deficits present in the individual divided by 38), with the FI ranging between 0 (no deficit) and 1 (all deficits). Although the FI is primarily treated as a continuous variable, subjects were divided by degree of frailty into 3 groups according to the FI score: non-frailty ($FI < 0.08$), pre-frailty ($0.08 \le FI < 0.25$), and frailty ($FI \ge 0.25$).[27,28]

Behavioral and Psychological Symptoms of Dementia

BPSD were evaluated by using the 28-item Dementia Behavior Disturbance Scale (DBD). Each subject was rated by his/her family or caregiver for frequency of each of the 28 items on a scale of 0–4 (0 = never, 1 = infrequent, 2 = sometimes, 3 = frequent, and 4 = always), with the sum of scores ranging from 0 to 112, where higher scores were assumed to indicate greater severity of BPSD.[29]

Caregiver Burden

Caregiver burden was assessed by using the Japanese version of the Zarit Burden Interview (J-ZBI),[30,31] consisting of 22 questions about the impact of a patient's disabilities on the lifestyle of his/her caregiver, including caregiver health, psychological well-being, finances, and social life and the relationship between the caregiver and the recipient of care. The patient's family or caregiver was instructed to rate how often the patient's disabilities affected their lifestyle (never = 0; rarely = 1; sometimes = 2; quite frequently = 3; and nearly always = 4), with the sum of scores ranging from 0 to 88, where higher scores were assumed to indicate a higher caregiver burden.

Other Variables

Information on the subjects' age, sex, education, marital status (married, never married, divorced, or widowed), living situation (with spouse, with family, or alone), and financial status (whether in need of financial support or not) was obtained from their clinical charts. The subjects were also assessed for their smoking status, drinking status, body mass index, and the number of medications they were on. Polypharmacy was defined as using 5 or more medications.[32] Basic ADL and instrumental ADL were assessed by using the Barthel Index[33] and Lawton Index.[34] Physical function was measured by using the Timed Up and Go Test (TUG), the reliability of which has been reported in individuals with cognitive impairment.[35,36] The subjects were also examined for potential confounders for BPSD and caregiver burden, which included cognitive status, vitality, depressive mood,

and nutritional status. Global cognitive status was assessed by using the Mini-Mental State Examination (MMSE).[37] Vitality was assessed by their caregivers using the Vitality Index (VI), a useful tool to measure vitality in elderly patients with dementia. VI is composed of 5 items (waking pattern, communication, feeding, on and off toilet, and rehabilitation and other activities), with each item assessed on a scale of 0–2 (2 = motivated, 1 = passive, and 0 = reluctant or indifferent) and with the VI ranging from 0 to 10 points, where 0 is assumed to indicate the lowest vitality.[38] Depressive mood was evaluated by the self-rated 15-item Geriatric Depression Scale (GDS).[39] The subjects' nutritional status was assessed by their caregivers using the Mini Nutritional Assessment Short-Form, with the score ranging from 0 to 14 to classify the subjects as having a normal nutritional status (score of 12–14), being at nutritional risk (score of 8–11), or having malnutrition (score of 0–7).[40] In the analysis, the patients at nutritional risk and those with malnutrition were analyzed as 1 group (malnutrition-risk group).

Statistical Analysis

In univariate analyses, the linear regression analyses were performed to explore the association of the FI and confounding variables (marital status, living situation, financial status, physical function, cognitive status, mood, nutritional status, and polypharmacy) with the DBD and the J-ZBI, given that these factors are shown to be associated with BPSD and/or caregiver burden.[7–14] In the multivariate analyses, multiple linear regression analyses were performed to investigate whether the FI was independently associated with the DBD or the J-ZBI, simultaneously adjusting for age, sex, education, and confounding variables. Since BPSD are known to be strongly associated with caregiver burden,[5,6] the DBD was entered in the multiple linear regression analysis to clarify the association of the FI with the J-ZBI. In addition, subanalyses were also performed by using the FI as a categorical variable (non-frail vs pre-frail or frail). In all linear multiple regression models, we assessed all independent variables for multicollinearity by calculating their variance inflation factor scores.

To better elucidate whether the relationship between the FI and increased caregiver burden was direct and/or mediated by increased BPSD, the SEM was performed using variables that were shown to be significantly associated with the DBD and/or the J-ZBI in multiple regression analyses. The accuracy of the SEM was determined by comparative fit index (CFI) and the root mean square error of approximation (RMSEA), which required that the value of the CFI be high (> 0.95) and that of the RMSEA be small (< 0.07) for a good fitting model.[41,42]

Finally, to conduct sensitivity analyses, we constructed FI-ADL impairments (15 variables), FI-geriatric syndromes (12 variables), and FI-comorbidities (11 variables) using the same variables as the original FI. As sensitivity analyses, then, we performed multiple regression analyses to investigate the relationship between these indices and the DBD or the J-ZBI, adjusting for age, sex, education, and MMSE scores.

Table 1. Clinical Characteristics of Subjects (N = 1,193)

Variable	Value
Age, mean ± SD, y	78.8 ± 6.3
Sex, female, n (%)	818 (68.6)
Education, mean ± SD, y	10.1 ± 2.6
Marital status, n (%)	
Married	688 (57.7)
Never married, divorced, or widowed	505 (42.3)
Living status, n (%)	
With spouse or family	1,016 (85.2)
Alone	177 (14.8)
Need for financial support, n (%)	107 (9.0)
Current smoker, n (%)	70 (5.9)
Current drinker, n (%)	346 (29.0)
Body mass index, kg/m^2, mean ± SD	21.9 ± 3.4
Barthel Index score, mean ± SD	95.5 ± 9.3
Lawton Index score, mean ± SD	
Male	3.1 ± 1.4
Female	5.3 ± 1.9
TUG, seconds, mean ± SD	13.0 ± 5.7
MMSE score, mean ± SD	18.9 ± 4.5
Vitality Index score, mean ± SD	8.8 ± 1.3
GDS-15 score, mean ± SD	4.4 ± 3.0
DBD score, mean ± SD	16.8 ± 11.3
J-ZBI score, mean ± SD	21.5 ± 14.9
MNA-SF score, mean ± SD	10.7 ± 2.3
Nutritional status, n (%)	
Normal nutritional status (score of 12–14)	464 (38.9)
At nutritional risk (score of 8–11)	612 (51.3)
Malnourished (score of 0–7)	117 (9.8)
No. of medications, mean ± SD	4.8 ± 3.5
Polypharmacy (≥ 5), n (%)	555 (46.5)
Frailty Index (FI; 0–1 scale), mean ± SD	0.16 ± 0.10
Pre-frailty (0.08 ≤ FI < 0.25), n (%)	663 (55.6)
Frailty (FI ≥ 0.25), n (%)	198 (16.6)

Abbreviations: DBD = Dementia Behavior Disturbance Scale, GDS = Geriatric Depression Scale, J-ZBI = Japanese version of Zarit Burden Interview, MMSE = Mini-Mental State Examination, MNA-SF = Mini Nutritional Assessment Short-Form, TUG = Timed Up and Go Test.

All statistical analyses were carried out by using STATA 14.0 (Stata Corp, College Station, Texas). *P* values < .05 were considered statistically significant.

RESULTS

The clinical profile of the subjects is shown in Table 1. The subjects had a mean ± SD age of 78.8 ± 6.3 years and a mean MMSE score of 18.9 ± 4.5. Of the 1,193 subjects, 818 (68.6%) were female. They had a mean FI score of 0.16 ± 0.10 (minimum–maximum = 0.00–0.66), with more than half of the subjects (n = 663; 55.6%) shown to be pre-frail and 198 (16.6%) shown to be frail. The subjects had a mean DBD score of 16.8 ± 11.3 and a mean J-ZBI score of 21.5 ± 14.9.

Table 2 shows the results of the linear regression analyses performed to examine the association between the FI and the DBD. In univariate analyses, the FI was significantly associated with the DBD (coefficient 46.30; 95% CI, 40.46 to 52.15; *P* < .001). Other factors associated with DBD were age, education, marital status, need for financial support, TUG, MMSE, VI, GDS, nutritional status, and polypharmacy (Table 2). In the multiple regression model, the FI remained significantly associated with the DBD (coefficient 34.22; 95% CI, 27.09 to 41.35; *P* < .001). Other independent factors

Table 2. Association Between the Frailty Index and DBD in the Linear Regression Analysis

	DBD						
	Unadjusted Model			Adjusted Model			
Variable	Coefficient (95% CI)	β	*P* Value	Coefficient (95% CI)	β	*P* Value	VIF
Frailty Index	46.30 (40.46 to 52.15)	0.41	<.001	34.22 (27.09 to 41.35)	0.30	<.001	1.73
Age	0.25 (0.15 to 0.35)	0.14	<.001	−0.03 (−0.13 to 0.07)	−0.02	.556	1.38
Female (ref male)	1.06 (−0.32 to 2.44)	0.04	.131	−0.08 (−1.4 to 1.24)	0.00	.906	1.28
Education	−0.41 (−0.65 to −0.17)	−0.10	.001	0.08 (−0.15 to 0.31)	0.02	.499	1.28
Never married, divorced, or widowed (ref married)	4.27 (2.99 to 5.54)	0.19	<.001	2.97 (1.60 to 4.35)	0.13	<.001	1.57
Living alone (ref with others)	1.28 (−0.52 to 3.07)	0.04	.164	−0.02 (−1.72 to 1.69)	0.00	.985	1.25
Need for financial support	4.22 (1.99 to 6.45)	0.11	<.001	1.45 (−0.49 to 3.39)	0.04	.144	1.05
TUG	0.32 (0.21 to 0.43)	0.16	<.001	−0.12 (−0.23 to −0.01)	−0.06	.033	1.33
MMSE	−0.80 (−0.94 to −0.66)	−0.32	<.001	−0.46 (−0.59 to −0.33)	−0.18	<.001	1.17
Vitality Index	−3.26 (−3.71 to −2.82)	−0.38	<.001	−1.91 (−2.37 to −1.45)	−0.22	<.001	1.26
GDS-15	0.40 (0.19 to 0.62)	0.11	<.001	−0.18 (−0.38 to 0.01)	−0.05	.064	1.13
Malnutrition risk (ref well-nourished)	4.32 (3.03 to 5.61)	0.19	<.001	1.92 (0.77 to 3.07)	0.08	.001	1.08
Polypharmacy (≥ 5)	1.93 (0.65 to 3.21)	0.09	.003	−0.50 (−1.67 to 0.67)	−0.02	.401	1.16

Abbreviations: DBD = Dementia Behavior Disturbance Scale, GDS = Geriatric Depression Scale, MMSE = Mini-Mental State Examination, ref = reference group, TUG = Timed Up and Go Test, VIF = variance inflation factor.

Table 3. Association Between the Frailty Index and J-ZBI in the Linear Regression Analysis

	J-ZBI						
	Unadjusted Model			Adjusted Model			
Variables	Coefficient (95% CI)	β	*P* Value	Coefficient (95% CI)	β	*P* Value	VIF
Frailty Index	59.38 (51.57 to 67.18)	0.40	<.001	19.79 (10.83 to 28.74)	0.13	<.001	1.86
Age	0.25 (0.12 to 0.38)	0.11	<.001	−0.05 (−0.17 to 0.08)	−0.02	.460	1.38
Female (ref male)	−1.23 (−3.05 to 0.60)	−0.04	.189	−2.46 (−4.06 to −0.87)	−0.08	.003	1.28
Education	−0.24 (−0.56 to 0.09)	−0.04	.155	0.22 (−0.07 to 0.50)	0.04	.132	1.28
Never married, divorced, or widowed (ref married)	4.18 (2.48 to 5.88)	0.14	<.001	1.03 (−0.65 to 2.70)	0.03	.230	1.60
Living alone (ref with others)	2.21 (−0.17 to 4.60)	0.05	.067	1.59 (−0.47 to 3.66)	0.04	.131	1.25
Need for financial support	10.23 (7.31 to 13.14)	0.20	<.001	6.60 (4.25 to 8.96)	0.13	<.001	1.05
TUG	0.48 (0.33 to 0.62)	0.18	<.001	0.02 (−0.11 to 0.15)	0.01	.796	1.34
MMSE	−0.85 (−1.04 to −0.67)	−0.25	<.001	−0.15 (−0.32 to 0.01)	−0.05	.062	1.22
Vitality Index	−4.35 (−4.94 to −3.76)	−0.38	<.001	−1.60 (−2.17 to −1.02)	−0.14	<.001	1.34
GDS-15	0.54 (0.26 to 0.82)	0.11	<.001	−0.10 (−0.34 to 0.13)	−0.02	.389	1.14
Malnutrition risk (ref well-nourished)	7.33 (4.35 to 10.32)	0.18	<.001	1.69 (0.29 to 3.09)	0.06	.018	1.09
Polypharmacy (≥ 5)	3.45 (1.76 to 5.14)	0.12	<.001	0.89 (−0.52 to 2.31)	0.03	.216	1.16
DBD	0.76 (0.70 to 0.83)	0.58	<.001	0.57 (0.50 to 0.64)	0.43	<.001	1.41

Abbreviations: DBD = Dementia Behavior Disturbance Scale, GDS = Geriatric Depression Scale, J-ZBI = Japanese version of Zarit Burden Interview, MMSE = Mini-Mental State Examination, ref = reference group, TUG = Timed Up and Go Test, VIF = variance inflation factor.

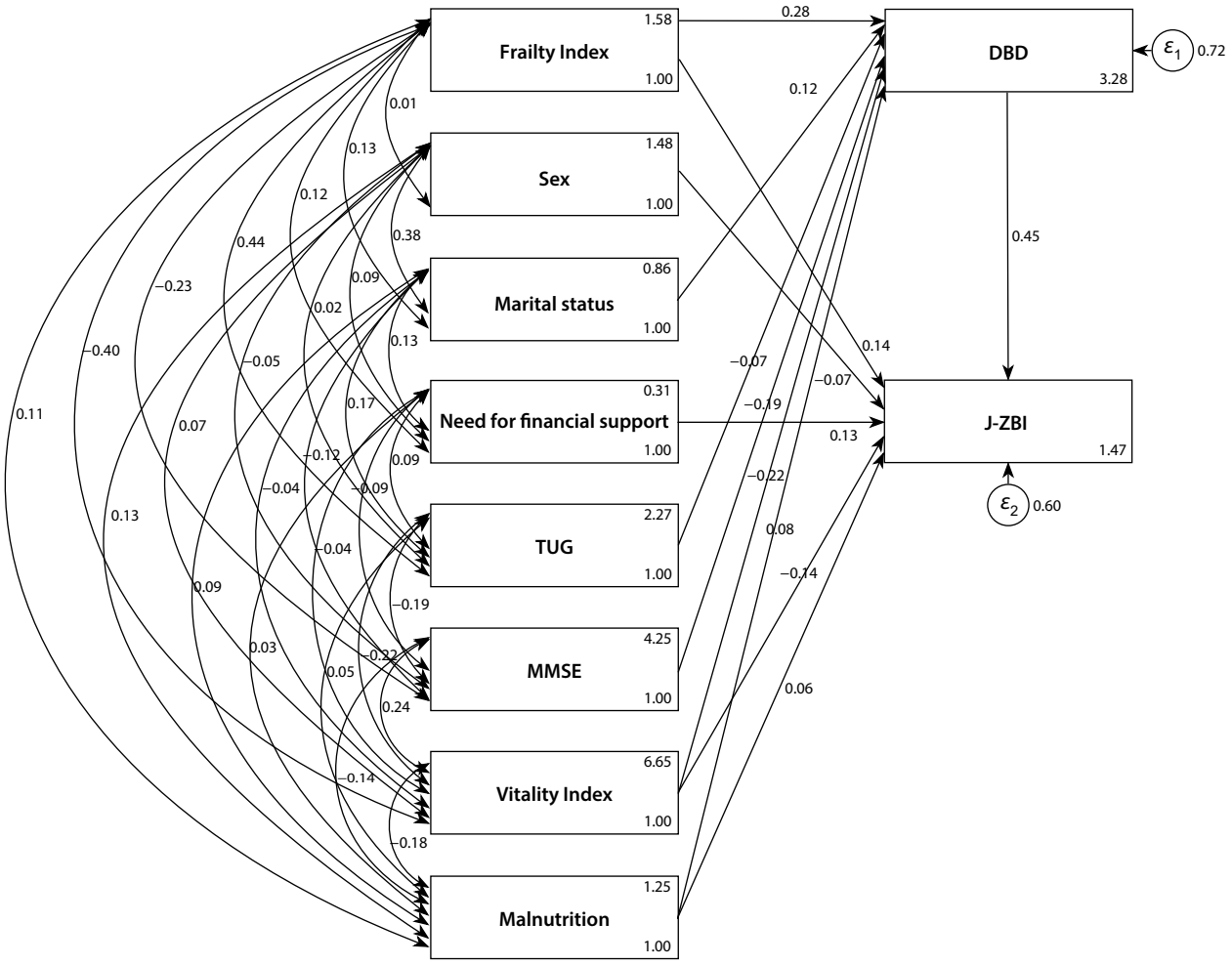
associated with DBD were marital status, TUG, MMSE, VI, and nutritional status (Table 2). When the FI was considered as a categorical variable, pre-frailty or frailty was associated with increased DBD scores (pre-frailty, coefficient 3.72; 95% CI, 2.31 to 5.12; $P < .001$; frailty, coefficient 8.34; 95% CI, 6.26 to 10.43; $P < .001$) (Supplementary Table 2).

Table 3 shows the results of the linear regression analyses performed to examine the association between FI and J-ZBI. In univariate analyses, the FI was significantly associated with the J-ZBI (coefficient 59.38; 95% CI, 51.57 to 67.18; $P < .001$). Other factors associated with the J-ZBI were age, marital status, need for financial support, TUG, MMSE, VI, GDS, nutritional status, polypharmacy, and DBD (Table 3). In the multiple regression model, the FI remained significantly associated with the J-ZBI (coefficient 19.79; 95% CI, 10.83 to 28.74; $P < .001$). Other independent factors associated with the J-ZBI were sex, need for financial support, VI, nutritional status, and DBD (Table 3). When the FI was considered as a categorical variable, pre-frailty or frailty was significantly associated with increased J-ZBI scores (pre-frailty, coefficient 2.56; 95% CI, 0.86 to 4.26; $P = .003$; frailty, coefficient 5.43; 95% CI, 2.86 to 7.99; $P < .001$) (Supplementary Table 3).

Based on these results, we hypothesized that the correlation between higher FI scores and increased caregiver burden scores was partially mediated by increased BPSD. In order to better elucidate the relationship between the FI, BPSD, and caregiver burden, a hypothetical model was generated by including variables that were shown to be significantly associated with the DBD and/or the J-ZBI in multiple regression analyses (Figure 1). Then, SEM was performed to provide estimates of the magnitude and significance of this hypothetical model. As a result, this hypothetical model provided an excellent fit to the observed data ($\chi^2_5 = 4.943$, $P = .423$; CFI = 1.000; RMSEA = 0.000). The direct and indirect effect of the FI and other factors on the J-ZBI is shown in Table 4. Both direct and indirect effect of the FI on the J-ZBI was shown to be significant (direct effect, $\beta = 0.14$, $P < .001$; indirect effect, $\beta = 0.13$, $P < .001$) (Table 4).

As sensitivity analyses, we created FI-ADL impairments, FI-geriatric syndromes, and FI-comorbidities to determine the contributions of these different deficits to the association

Figure 1. Results in the Structural Equation Model of Association Among the Frailty Index, DBD, J-ZBI, and Other Confounding Factors[a]



[a]$X^2_5 = 4.943$ ($P = .423$), RMSEA = 0.000, CFI = 1.000.
Abbreviations: CFI = comparative fit index, DBD = Dementia Behavior Disturbance Scale, J-ZBI = Japanese version of Zarit Burden Interview, MMSE = Mini-Mental State Examination, RMSEA = root mean square error of approximation, TUG = Timed Up and Go Test.

of physical frailty with BPSD or caregiver burden. Multiple regression analyses demonstrated that all 3 indices were significantly associated with the DBD (FI-ADL impairments, coefficient 29.12; 95% CI, 25.65 to 32.69; $P < .001$; FI-geriatric syndromes, coefficient 7.66; 95% CI, 3.63 to 11.68; $P < .001$; FI-comorbidities, coefficient 6.47; 95% CI, 0.99 to 11.95; $P = .021$) and the J-ZBI (FI-ADL impairments, coefficient 38.92; 95% CI, 34.08 to 43.76; $P < .001$; FI-geriatric syndromes, coefficient 11.28; 95% CI, 5.83 to 16.74; $P < .001$; FI-comorbidities, coefficient 8.35; 95% CI, 0.93 to 15.77; $P = .027$).

Table 4. Direct, Indirect, and Total Effect Estimates of the Frailty Index and Confounding Variables on J-ZBI Mediated by Severity of Behavioral and Psychological Symptoms of Dementia

	J-ZBI					
	Direct Effect		Indirect Effect		Total Effect	
Variables	β	*P* Value	β	*P* Value	β	*P* Value
Frailty Index	0.14	< .001	0.13	< .001	0.26	< .001
Female (ref male)	−0.07	.003	…	…	−0.07	.003
Never married, divorced, or widowed (ref married)	…	…	0.06	< .001	0.06	< .001
Need for financial support	0.13	< .001	…	…	0.13	< .001
TUG	…	…	−0.03	.020	−0.03	.020
MMSE	…	…	−0.08	< .001	−0.08	< .001
Vitality Index	−0.14	< .001	−0.10	< .001	−0.24	< .001
Malnutrition	0.06	.014	0.04	.001	0.09	< .001
DBD	0.45	< .001	…	…	0.45	< .001

Abbreviations: DBD = Dementia Behavior Disturbance Scale, J-ZBI = Japanese version of Zarit Burden Interview, MMSE = Mini-Mental State Examination, ref = reference group, TUG = Timed Up and Go Test.
Symbol: … = based on the hypothetical model used, direct or indirect effect not calculated for this variable.

DISCUSSION

The present study examined the association between deficits, as determined by the FI, BPSD, and caregiver burden. This is the first report to show that the FI is

associated with increased BPSD and caregiver burden in elderly patients with AD. Moreover, when the FI was considered as a categorical variable, even pre-frailty was associated with increased BPSD and caregiver burden.

To our knowledge, no preceding studies examined the association between the FI and BPSD. Some previous studies, however, demonstrated that impairment of ADL, which forms part of the FI, is associated with increased BPSD in patients with mild cognitive impairment (MCI) and dementia.[9,11,15] Comorbidities, as components of the FI, are also shown to be associated with BPSD. Moon et al[10] reported that the presence of hypertension and asymptomatic stroke were associated with the severity of apathy and depression in AD. Another study[12] also showed the significant association of a history of hypertension and stroke with some specific neuropsychiatric symptoms, including delusions, anxiety, agitation, and aggression. Of note, hypertension is shown to be a consistent risk factor for white matter hyperintensity,[43] which is, in turn, shown to be associated with increased BPSD in AD.[44,45] These previous studies indicate that deficits, such as impairment of ADL and comorbidities, influence the occurrence and severity of individual BPSD in AD independently of cognitive decline. The present study appears not only to support these earlier reports but to suggest further that BPSD might increase even in pre-frailty and increase in proportion to increased deficits.

In patients with dementia, BPSD are known to be strongly associated with caregiver burden.[5,6] The present study also showed a significant association between DBD and J-ZBI scores. However, the FI was significantly associated with caregiver burden independently of BPSD. Moreover, the SEM demonstrated that both direct and indirect effects via BPSD of the FI on the J-ZBI were significant. In this context, some studies suggested that adequate management of BPSD could prevent caregiver burden from increasing. Dauphinot et al[46] showed that caregiver burden assessed by the ZBI tended to decrease when BPSD decreased during a mean follow-up of 12.6 months, although this decrease failed to achieve significance. Conde-Sala et al[47] also found that neuropsychiatric symptoms increased among AD patients with increased ZBI scores during 3-year follow-up. Conversely, in those with decreased ZBI scores, neuropsychiatric symptoms decreased during 3-year follow-up. Together with these reports, our results suggest that, using the FI as an objective marker of deficit accumulation, intervention aimed at decreasing deficits could represent a successful strategy in the adequate management of BPSD, thus preventing caregiver burden from increasing. Further longitudinal studies are required to elucidate the correlation between decrease of deficits, BPSD, and caregiver burden.

In sensitivity analyses, although FI-ADL impairments, FI-geriatric syndromes, and FI-comorbidities were associated with BPSD and caregiver burden, FI-ADL impairments showed a relatively strong correlation compared to the other 2 indices. The FI, which combines these different deficits, is a useful predictor of cognitive decline, hospitalization, and mortality in AD patients.[22,24] The FI, however, may have a methodological limitation in that higher FI scores may represent more severe stages of dementia, since impairments in ADL have been related to severity of dementia. Severe stages of dementia may contribute to these adverse outcomes. Thus, while we adjusted for MMSE score as a covariate accounting for disease stage, it is possible that the severity of dementia may have affected the significant links between FI and BPSD or caregiver burden. Nevertheless, these sensitivity analyses emphasize that the accumulation of small deficits, or pre-frailty, could contribute to BPSD and caregiver burden.

This study has several limitations. First, since this was a cross-sectional study, it remains unclear whether the FI has a clear temporal association with BPSD and caregiver burden. Second, many subjects were excluded from the study because of missing data, and their exclusion may have biased our results. Finally, our study lacked information on the caregivers' characteristics, such as age, sex, level of education, income status, and psychological factors, particularly given that these caregiver-related factors have been proposed as factors associated with caregiver burden.[5,6]

CONCLUSION

Deficits as determined by the FI were associated with increased BPSD and caregiver burden. Longitudinal studies are required to further clarify the association between the FI, BPSD, and caregiver burden, as well as to provide a basis for devising successful strategies for reducing BPSD and caregiver burden in AD.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Physical Frailty Correlates With Behavioral and Psychological Symptoms of Dementia and Caregiver Burden in Alzheimer's Disease

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List of Supplementary Material for the article

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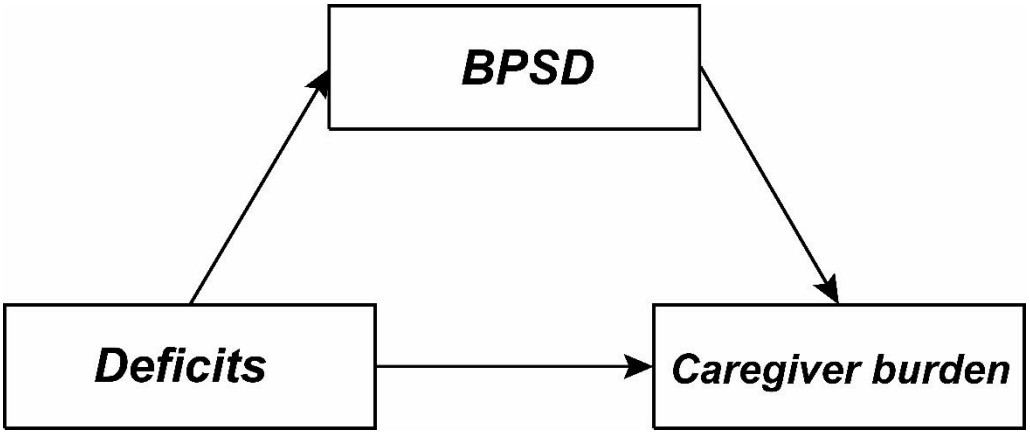

Supplementary Figure 1. Conceptual model of our hypothesis.

We hypothesized that cumulative deficits have both direct and indirect effects (mediated through increased BPSD) on caregiver burden.

Abbreviations: BPSD, behavior and psychiatric symptoms of dementia.

Supplementary Table 1. List of variables used for the construction of Frailty Index and their prevalence

Variables	Prevalence
Difficulty eating	3.2
Difficulty moving between wheelchair and bed	3.9
Difficulty grooming	7.1
Difficulty using toilet	3.9
Difficulty bathing	9.6
Difficulty walking around the house	5.7
Difficulty moving up/down stairs	8.9
Difficulty dressing	7.7
Fecal incontinence	14.2
Urinary incontinence	20.2
Difficulty using telephone	7.1
Difficulty shopping	63.8
Difficulty using transportation	37.0
Difficulty taking medications	67.2
Difficulty managing finances	14.3
Dyspnea	7.4
Chest pain	10.3
Edema	22.2
Fatigue	27.4
Fever	3.2
Speech disturbance	12.2
Syncope	5.4
Headache	18.2
Ringing in the ears	14.3
Mastication disorder	7.2

Itching	19.9
Lumbago pain	35.0
Liver disease	2.0
Cardiac disease	12.7
Cancer	7.6
Hypertension	57.3
Pulmonary disease	4.3
Dyslipidemia	33.4
Depression	3.9
Kidney disease	1.9
Diabetes mellitus	17.1
Stroke	4.3
Insomnia	3.9

Supplementary Table 2. Association between frailty and DBD according to linear regression analysis.

	DBD						
	Unadjusted model			Adjusted model			
Variables	coefficient (95% CI)	*β*	*P* value	coefficient (95% CI)	*β*	*P* value	VIF
Frailty status (ref. non-frailty)							
Pre-frailty	5.47 (4.09 to 6.85)	0.24	< 0.001	3.72 (2.31 to 5.12)	0.16	< 0.001	1.62
Frailty	13.04 (11.20 to 14.88)	0.43	< 0.001	8.34 (6.26 to 10.43)	0.28	< 0.001	2.00
Age	0.25 (0.15 to 0.35)	0.14	< 0.001	-0.01 (-0.11 to 0.09)	-0.01	0.816	1.38
Female (ref. male)	1.06 (-0.32 to 2.44)	0.04	0.131	0.07 (-1.26 to 1.41)	0.00	0.916	1.28
Education	-0.41 (-0.65 to -0.17)	-0.10	0.001	0.11 (-0.12 to 0.35)	0.03	0.354	1.28
Never married, divorced or widowed (ref. Married)	4.27 (2.99 to 5.54)	0.19	< 0.001	2.99 (1.60 to 4.38)	0.13	< 0.001	1.57
Living alone (ref. with others)	1.28 (-0.52 to 3.07)	0.04	0.164	-0.19 (-1.91 to 1.53)	-0.01	0.827	1.25
Need for financial support	4.22 (1.99 to 6.45)	0.11	< 0.001	1.77 (-0.19 to 3.73)	0.04	0.077	1.04
TUG	0.32 (0.21 to 0.43)	0.16	< 0.001	-0.05 (-0.16 to 0.05)	-0.03	0.333	1.28
MMSE	-0.80 (-0.94 to -0.66)	-0.32	< 0.001	-0.46 (-0.60 to -0.33)	-0.18	< 0.001	1.17
Vitality Index	-3.26 (-3.71 to -2.82)	-0.38	< 0.001	-2.08 (-2.54 to -1.62)	-0.24	< 0.001	1.24
GDS-15	0.40 (0.19 to 0.62)	0.11	< 0.001	-0.10 (-0.29 to 0.10)	-0.03	0.332	1.11
Malnutrition-risk (ref. well-nourished)	4.32 (3.03 to 5.61)	0.19	< 0.001	1.95 (0.78 to 3.11)	0.08	0.001	1.08
Polypharmacy (≥ 5)	1.93 (0.65 to 3.21)	0.09	0.003	-0.22 (-1.41 to 0.97)	-0.01	0.712	1.18

Abbreviations: DBD, dementia behavior disturbance scale; GDS, geriatric depression scale; MMSE, mini-mental state examination; TUG, timed up and go test; VIF, variance inflation factor.

Supplementary Table 3. Association between frailty and J-ZBI according to linear regression analysis.

	J-ZBI						
	Unadjusted model			Adjusted model			
Variables	coefficient (95%CI)	*β*	*P* value	coefficient (95% CI)	*β*	*P* value	VIF
Frailty status (ref. non-frailty)							
Pre-frailty	7.36 (5.53 to 9.19)	0.24	< 0.001	2.56 (0.86 to 4.26)	0.09	0.003	1.66
Frailty	17.12 (14.67 to 19.57)	0.43	< 0.001	5.43 (2.86 to 7.99)	0.14	< 0.001	2.11
Age	0.25 (0.12 to 0.38)	0.11	< 0.001	-0.04 (-0.16 to 0.08)	-0.02	0.518	1.38
Female (ref. male)	-1.23 (-3.05 to 0.60)	-0.04	0.189	-2.34 (-3.95 to -0.74)	-0.07	0.004	1.28
Education	-0.24 (-0.56 to 0.09)	-0.04	0.155	0.24 (-0.05 to 0.52)	0.04	0.104	1.28
Never married, divorced or widowed (ref. Married)	4.18 (2.48 to 5.88)	0.14	< 0.001	1.01 (-0.67 to 2.69)	0.03	0.237	1.60
Living alone (ref. living with others)	2.21 (-0.17 to 4.60)	0.05	0.067	1.50 (-0.57 to 3.56)	0.04	0.155	1.25
Need for financial support	10.23 (7.31 to 13.14)	0.20	< 0.001	6.74 (4.39 to 9.09)	0.13	< 0.001	1.05
TUG	0.48 (0.33 to 0.62)	0.18	< 0.001	0.05 (-0.08 to 0.18)	0.02	0.452	1.28
MMSE	-0.85 (-1.04 to -0.67)	-0.25	< 0.001	-0.15 (-0.31 to 0.02)	-0.04	0.075	1.22
Vitality Index	-4.35 (-4.94 to -3.76)	-0.38	< 0.001	-1.64 (-2.22 to -1.07)	-0.15	< 0.001	1.32
GDS-15	0.54 (0.26 to 0.82)	0.11	< 0.001	-0.06 (-0.29 to 0.17)	-0.01	0.600	1.11
Malnutrition-risk (ref. well-nourished)	7.33 (4.35 to 10.32)	0.18	< 0.001	1.67 (0.27 to 3.08)	0.05	0.019	1.09
Polypharmacy (≥ 5)	3.45 (1.76 to 5.14)	0.12	< 0.001	0.91 (-0.51 to 2.34)	0.03	0.209	1.18

DBD	0.76 (0.70 to 0.83)	0.58	< 0.001	0.58 (0.51 to 0.65)	0.44	< 0.001	1.38

Abbreviations: DBD, dementia behavior disturbance scale; GDS, geriatric depression scale; J-ZBI, Japanese version of zarit burden interview; MMSE, mini-mental state examination; TUG, timed up and go test; VIF, variance inflation factor.