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Research Article

# Subtypes of Late-Life Depression: A Data-Driven Approach on Cognitive Domains and Physical Frailty

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## Abstract

**Background:** With increasing age, symptoms of depression may increasingly overlap with age-related physical frailty and cognitive decline. We aim to identify late-life-related subtypes of depression based on measures of depressive symptom dimensions, cognitive performance, and physical frailty.

**Methods:** A clinical cohort study of 375 depressed older patients with a DSM-IV depressive disorder (acronym NESDO). A latent profile analysis was applied on the three subscales of the Inventory of Depressive Symptomatology, as well as performance in five cognitive domains and two proxies for physical frailty. For each class, we investigated remission, dropout, and mortality at 2-year follow-up as well as change over time of depressive symptom severity, cognitive performance, and physical frailty.

**Results:** A latent profile analysis model with five classes best described the data, yielding two subgroups suffering from pure depression (“mild” and “severe” depression, 55% of all patients) and three subgroups characterized by a specific profile of cognitive and physical frailty features, labeled as “amnesic depression,” “frail-depressed, physically dominated,” and “frail-depressed, cognitively dominated.” The prospective analyses showed that patients in the subgroup of “mild depression” and “amnesic depression” had the highest remission rates, whereas patients in both frail-depressed subgroups had the highest mortality rates.

**Conclusions:** Late-life depression can be subtyped by specific combinations of age-related clinical features, which seems to have prospective relevance. Subtyping according to the cognitive profile and physical frailty may be relevant for studies examining underlying disease processes as well as to stratify treatment studies on the effectiveness of antidepressants, psychotherapy, and augmentation with geriatric rehabilitation.

**Keywords:** Depression, Cognitive aging, Frailty

Late-life depression is one of the most common psychiatric disorders in later life (1). With increasing age, depressive disorder becomes more often chronic and treatment resistant (2). One explanation can be found in the association between depressive disorder and senescence (3). Whereas aging refers to the chronological passage of time, senescence refers to biological aging or the gradual deterioration of

functional characteristics and their underlying physiological processes (4). In contrast to aging, senescence can be a dynamic, reversible process. For example, accelerated telomere length shortening can partly be reversed by telomerase (5). Depressive disorder has been associated with all levels of senescence, including the molecular level, such as DNA damage and mitochondrial dysfunction (6); the

cellular level, such as telomere attrition, protein accumulation, and abnormal secretory patterns (7,8); the tissue and system level, such as sarcopenia and metabolic dysregulation (9,10); and finally the clinical level, such as frailty, vascular disease, and dementia (11–13). Because senescence accumulates with age and the diagnostic criteria of a depressive disorder partly overlap with cognitive and physical features of (comorbid) nonpsychiatric diseases, the clinical phenotype and underlying pathophysiology of depressive disorder becomes more heterogeneous during aging.

Physical frailty and cognitive decline, both concepts at the clinical level of senescence, are closely related to late-life depression. Physical frailty reflects a critical decrease of the functional and physiological reserves of multiple organic systems placing persons at risk of negative health outcomes in the presence of even mild stressors (14). Depression and frailty are reciprocally related (11). Moreover, physical frailty predicts chronicity of depressive symptoms over time in the general population (15,16) as well as nonremission of older patients with a depressive disorder (17). Likewise, depressive disorder is bidirectionally associated with deficits in multiple cognitive domains (18,19), comparable to aging-related cognitive decline. Moreover, cognitive deficits in late-life depression mainly persist after remission of depression (20,21), and in particular, low processing speed and executive dysfunction predict a protracted course of the depression (22,23).

From a clinical perspective, it would be important to recognize subtypes of late-life depression, as patients with specific subtypes may differ in their risk of adverse health outcomes as well as response to treatment. For example, Selective serotonin reuptake inhibitors (SSRIs) have been shown to be less effective among depressed patients with executive dysfunctioning (23,24). Efforts to delineate specific subtypes of late-life depression have either focused on specific (aging-related) pathophysiological mechanisms (eg, depression in Alzheimer's disease (25), vascular depression (26)) or were limited to additional diagnostic features being either cognitive features (eg, depression-executive dysfunctioning syndrome (27,28)) or physical frailty (eg, frail-depressed subtype (29)). Thus far, aging-related physical and cognitive features have never been included simultaneously in studies that tried to identify late-life depression subtypes (eg, (30–32)). Moreover, aging-related features have hardly been taken into account in treatment studies on late-life depression (33).

The objective of the present study is to identify late-life-related subtypes of depression based on the clinical level of senescence combining depressive symptom dimensions, physical frailty parameters, and cognitive deficits using a data-driven approach.

## Methods

### Participants and Procedures

The present study used data from the Netherlands Study of Depression in Older people (NESDO), a cohort study aimed to examine the course and consequences of depressive disorders in older persons. Details of the study design and rationale of NESDO have been described in previous publications (34,35), but are summarized briefly. Inclusion criteria were age  $\geq 60$  years and meeting the criteria for a DSM-IV depressive disorder diagnosis using the Composite International Diagnostic Interview (version 2.1). Exclusion criteria were (i) dementia, defined as an established diagnosis of dementia, suspected for dementia according to a geriatric psychiatrist, or a Mini-Mental State Examination score (MMSE) under 18; (ii) a history of an organic, psychotic, or bipolar disorder; and/or (iii) insufficient mastery of the Dutch language.

Participants underwent a baseline examination, including the Composite International Diagnostic Interview (version 2.0), physical examination, cognitive testing, and several observer and self-report questionnaires, at one of the five research locations or at the homes of the participants. All baseline characteristics amenable to change were also administered at 2-year follow-up. Every 6 months, postal questionnaires were sent to monitor, among other measures, depressive symptom severity (34). For the present study, we considered the inventory of depressive symptoms, gait speed, handgrip strength, and various cognitive tests at baseline as profiling parameters, as described below in more detail.

Of the 378 depressed patients included, 359 (95.0%) had a (past 6-month) major depressive disorder, 100 (26.5%) had dysthymia, and 21 (5.6%) had a (past-month) minor depression. A total of 285 patients participated in the 2-year follow-up, of which 147/285 (51.6%) were classified as remitted depression defined as no past-month minor or past 6-month major depression or dysthymia at follow-up.

The ethical review boards of all participating study centers approved the study protocol of NESDO, and all participants provided written informed consent.

### Depressive Symptom Severity

The severity of depressive symptoms was assessed with the self-report version of the Inventory of Depressive Symptomatology (IDS-SR). Instead of the sum score reflecting overall depression severity, we used the three subscales reflecting a mood (nine items), motivational (five items), and somatic-affective symptom dimension (eight items; for detailed information on the subscales, see ref. (36)). The IDS-SR was administered at baseline and 2-year follow-up, as well as in between at 6-month intervals using postal questionnaires.

### Physical Frailty Measures

We assessed handgrip strength and gait speed at baseline and follow-up (37). Handgrip strength (weakness) was assessed with the JAMAR hydraulic hand dynamometer. Participants were asked to perform two squeezes with the dynamometer, in standing position, using their dominant hand. The best performance, recorded as strength in kilograms, was used for analysis. Gait speed was measured over a 6-m walking course. In all figures and tables, we present the number of seconds to complete the walking course as indicator of gait speed.

### Cognitive Functioning

Cognitive functioning was measured with three cognitive tests administered at baseline and 2-year follow-up, resulting in five cognitive domains, as described previously and summarized below (19).

#### Auditory Verbal Learning Test

A modified version limited to a list of 10 common nouns, of which participants were asked to recall as many as possible immediately after a research assistant read them aloud in five successive trials. After 20 minutes, the participants were asked to recall the words again. In the analyses, we included both the verbal memory delayed recall score (range 0–10) and the immediate memory score, that is, the sum score of the five trials (range 0–50).

#### Stroop Color-Word Test

An abbreviated version of the Stroop Color-Word Test was used to minimize patient burden. The Stroop Color-Word Test

consists of three subtasks. First, participants read words (card I: the words “red, blue, green, or yellow” printed in black). Second, participants have to name the colors on a card (card II: colored patches in red, blue, green, or yellow) aloud as fast and accurate as possible. The total number of seconds to complete these Stroop I (tI) and Stroop II (tII) tests is an index of processing speed. In the Stroop III (tIII) test, patients have to read the words red, blue, green, or yellow, printed in incongruently colored ink. The interference score is calculated by the following formula:  $(tIII - 0.5 \times (tI + tII)) / (0.5 \times (tI + tII))$  (tIII = time in seconds for the third card).

### Digit Span

Digit Span is a subtest from the Wechsler Adult Intelligence Scale (WAIS). Participants were asked to repeat a series of digits in a forward order or in reverse order. After every correct series, a longer series of digits was presented, adding one digit each time. The longest series of digits a participant could repeat in forward (range 0–12) or reverse order (range 0–10) were used. A measure of the cognitive domain of working memory was calculated by adding the total number of correct items of the forward and backward scores.

### Covariates

Age, level of education, and sex were assessed during the baseline interview. The number of chronic diseases was assessed by well-validated 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/arthrosis, and cancer) (38).

### Statistical Analyses

In case of a skewed distribution, data were transformed when necessary. Interference score was positively skewed, but normally distributed after taking the natural logarithm of the original value + 50. Gait speed and processing speed were positively skewed but were normally distributed after being transformed by the inverse (1/time in seconds).

Latent profile analysis (LPA) was used to identify the optimal number of latent classes to describe the interpersonal heterogeneity in patterns of 10 distinct clinical dimensions that correlated less than 0.60. To this end, we used the standardized scores of three depressive symptom dimensions (mood, somatic, and motivation), two distinct proxies for physical frailty (handgrip strength and gait speed), and five domains of cognitive performance (processing speed, interference score, working memory, immediate memory, and delayed recall) at baseline as input variables in the LPA. LPA was run using a robust maximum likelihood estimator in the Mplus 5.0 statistical software package (39). Models with increasing numbers of classes were estimated and compared. The optimal model was selected using the Akaike information criterion and Bayesian information criterion, with the lowest values indicating the model that best describes the data. In addition, the bootstrapped likelihood ratio test was used to test whether adding a *k*th class to a *k*-class model significantly improved model fit. Out of practical considerations (ie, interpretability and statistical power in subsequent class comparison analyses), the minimum class size of the smallest class was also considered for each model.

All LPAs were run with multiple random starts to avoid identification of a model at a local maximum.

Cross-sectional differences on baseline characteristics between the LPA classes were investigated with Pearson  $\chi^2$  tests for discrete variables or Mann–Whitney *U* tests for continuous variables.

We performed a multinomial regression analysis to evaluate the association between LPA class membership and outcome parameters at 2-year follow-up, that is, depression outcome (remission yes/no), dropout, and mortality.

Subsequently, we examined the change of the profiling parameters over time, in order to interpret the different classes identified by the LPA. We used repeated-measures analysis of variance to investigate the association between LPA classes and frailty and cognitive outcomes at 2-year follow-up. Because the IDS-SR was administered more than twice, we applied linear mixed modeling to investigate whether classes showed different prospective trajectories of mean IDS-SR severity scores over time. All prospective analyses were adjusted for baseline age, level of education, sex, number of chronic diseases, as each of these is known to be associated with either depression, cognitive functioning, and frailty.

Finally, although patients with (suspected) dementia were excluded at baseline, we cannot exclude the possibility of undetected dementia among patients with an MMSE score between 18 and 24. Therefore, we performed sensitivity analyses by excluding 23 patients who scored below 25 on the MMSE.

All these analyses were conducted with SPSS (version 25).

## Results

### Study Participants

Of the 378 depressed patients, we included 375 persons in the LPA at baseline. We excluded one patient based on an MMSE score of 17 and two patients with extreme *Z*-scores on the cognitive and frailty tests (>8) who were consistently allocated to one small separate class.

The 375 included patients had a median age of 69 years and 66.1% were females. A total of 285 patients (76.0%) participated in the 2-year follow-up visits. Of the 90 persons who did not have follow-up data, 25 persons were deceased at follow-up. As given in Table 1, persons with no data at follow-up had worse baseline scores on the cognitive tests (processing speed, working memory, and verbal memory) and handgrip strength.

### Latent Profile Analysis

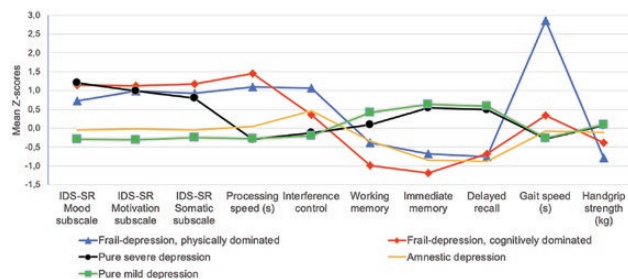
The LPA showed that the model with five classes best described the data (Akaike information criterion = 9,244, Bayesian information criterion = 9,495). Although the six-class solution had a lower Bayesian information criterion value (9,425), this solution was not chosen as some of the classes were very small (<5% of the participants). Figure 1 presents the characterization of the five classes graphically. The *Z*-scores of cognitive dimensions are recoded in a way that higher scores represent better performance. Because the different depressive symptom dimensions did not contribute to the subtyping, the IDS sum score was used in all further analyses. Three classes were characterized by severe depressive symptoms and two classes by mild depressive symptoms. Table 2 presents the characterization of the five classes numerically, including post hoc tests (significance level set at .01 to adjust for multiple testing).

Post hoc tests showed that both classes with mild depressive symptoms significantly differed on all dimensions except handgrip

**Table 1.** Baseline Characteristics, Missing Data on Follow-up

Characteristics	Total Sample (N = 375)	Missing (n = 90)	Data Present (n = 285)	Statistics (Cases With Missing vs Present Data)
<b>Sociodemographics</b>				
Age (y), M (IQR)	69 (11)	70 (10)	69 (12)	$U = 12,194.5, p = .481$
Female sex (yes), <i>n</i> (%)	248 (66.1)	61 (67.8)	187 (65.6)	$\chi^2 = 0.14, df = 1, p = .705$
Education (y), M (IQR)	10 (3)	10 (6)	10 (3)	$U = 14,217.5, p = .116$
<b>Psychopathology</b>				
Total IDS-SR score, M (IQR)	29.5 (19.0)	30.0 (20.0)	29.0 (19.0)	$U = 11,629.5, p = .374$
IDS-SR mood subscale, M (IQR)	8.0 (8.0)	9.0 (9.0)	8.0 (7.0)	$U = 11,458.5, p = .299$
IDS-SR motivation subscale, M (IQR)	5.0 (4.0)	5.0 (5.0)	5.0 (5.0)	$U = 10,885.5, p = .244$
IDS-SR somatic subscale, M (IQR)	9.0 (6.0)	9.0 (6.0)	9.5 (6.0)	$U = 12,569.5, p = .853$
Major depression (yes), <i>n</i> (%)	356 (94.9)	86 (95.6)	270 (94.7)	$\chi^2 = 0.10, df = 1, p = .758$
<b>Cognitive functioning</b>				
Processing speed (s), M (IQR)	45.0 (11.0)	48.0 (13.0)	44.0 (10.5)	$U = 954.0, p = .005$
Interference, M (IQR)	120.7 (68.8)	128.0 (87.2)	118.2 (63.1)	$U = 10,473.0, p = .196$
Working memory, M (IQR)	13.0 (5.0)	12.0 (5.0)	13.0 (5.0)	$U = 14,113.5, p = .015$
Total immediate memory, M (IQR)	32.0 (11.0)	31.0 (9.0)	33.0 (10.0)	$U = 15,252.5, p = .003$
Delayed recall, M (IQR)	6.0 (4.0)	5.0 (4.0)	6.0 (3.0)	$U = 15,849.5, p = .000$
<b>Physical functioning</b>				
Gait speed (s), M (IQR)	6.0 (3.0)	6.0 (3.0)	6.0 (3.0)	$U = 10,845.0, p = .132$
Handgrip strength (kg), M (IQR)	26.0 (14.0)	24.0 (12.0)	27.0 (14.0)	$U = 14,491.0, p = .024$
Number of chronic diseases, M (IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)	$U = 12,390.5, p = .655$

Notes: M = median; IQR = interquartile range (difference between the upper and the lower quartiles); IDS-SR = Inventory of Depressive Symptoms—Self-Report scale; Mann-Whitney *U*-test, Pearson's chi-squared test ( $\chi^2$ ).

**Figure 1.** Class characteristics of the five classes.

strength (see Table 2). Nonetheless, only large differences ( $>0.8$  Z-score) were found with respect to immediate and delayed memory function (see Figure 1). These classes could be labeled as “mild pure depression” ( $n = 121, 32.3\%$ ) and “amnesic depression” ( $n = 104, 27.7\%$ ).

Post hoc tests revealed that depressive symptom severity did not differ between the three severely depressed classes. Of these classes, one class performed well with respect to cognitive and physical functioning and was labeled “severe pure depression” ( $n = 85, 22.7\%$ ). Post hoc tests showed that, except with respect to working memory, this class performed significantly better on all cognitive domains and frailty measures compared with both other severely depressed classes (see Table 2). The other two severely depressed classes had the worst overall level of cognitive performance and the lowest scores on both frailty measures (see Table 2 and Figure 1). Because these two so-called “frail-depressed” classes differed only significantly with respect to gait speed (see Table 2), we labeled them as “frail-depressed, cognitively dominated” ( $n = 45, 12.0\%$ ) and “frail-depressed, physically dominated” ( $n = 20, 5.3\%$ ).

## Outcome of Depressive Disorder, Dropout, and Mortality at 2-Year Follow-up

Adjusted for covariates, LPA class membership was significantly associated with outcome at follow-up ( $\chi^2 = 30.4, df = 12, p = .002$ , see Figure 2). Because we have identified two pure depressed classes, both pure depressed classes were used as a reference class for the other classes.

Compared with the mild pure depressed class, patients in the “frail-depressed, cognitively dominated” class had higher odds of depression at 2 years (odds ratio [OR] = 3.1 [95% confidence interval [CI]: 1.14–8.41],  $p = .027$ ), dropout (OR = 6.3 [95% CI: 2.04–19.2],  $p = .001$ ), and mortality (OR = 7.2 [95% CI: 1.7–30.4],  $p = .007$ ), and compared with the severe pure depressed class also a higher odds of dropout (OR = 3.4 [95% CI: 1.03–11.0],  $p = .044$ ) and mortality (OR = 5.8 [95% CI: 1.1–31.7],  $p = .041$ ). The amnesic depressed class had only a significantly lower odds of depression at follow-up compared with the severe pure depressed class (OR = 0.3 [95% CI: 0.1–0.6],  $p = .001$ ). The frail-depressed, physically dominated class did not differ compared with any of the pure depressed classes.

## Change of Profile Parameters Over Time—Depressive Symptoms

The course of depressive symptom severity was best described by a linear mixed model with an unstructured covariance structure (ie, lowest Bayesian information criterion value). The trajectories of depressive symptom severity over time differed significantly across classes (interaction of class membership by time:  $F(4,312.5) = 12.6, p < .001$ ).

Compared with the mild pure depressed class, both frail-depressed classes (physically dominated:  $t = -3.6, df = 305.7, p < .001$ ; cognitively dominated:  $t = -4.5, df = 327.4, p < .001$ ) and the



**Table 2.** Baseline Characteristics, Stratified by Latent Profile Analysis Group Assignment

Characteristics	Total Sample (N = 375)	Pure, Mild Depression (A) (n = 121)	Pure, Severe Depression (B) (n = 85)	Amnesic Depression (C) (n = 104)	Frail-Depression, Physically Dominated (D) (n = 20)	Frail-Depression, Cognitively Dominated (E) (n = 45)	Post hoc Analyses ( <i>p</i> < .01), Difference Between LPA Classes*
<b>Sociodemographics</b>							
Age (y), M (P)	69 (65–76)	68 (64–75)	65 (62–70)	73 (69–79)	79 (75–84)	70 (66–76)	A<B,C; B<C,D,E; D>E
Female sex (yes), n (%)	248 (66.1)	86 (71.1)	54 (63.5)	60 (57.7)	18 (90.0)	30 (66.7)	C<D
Education (y), M (P)	10 (9–12)	10 (9–15)	10 (9–15)	10 (9–11)	10 (6–12)	9 (6–10)	A>E; B>C,E; C>D
Total IDS-SR score, M (P)	30 (20–39)	20 (15–26)	40 (36–46)	26 (18–30)	40 (28–50)	43 (38–52)	A<B,C,D,E; B>C; C<D,E
Major depression (yes)**, n (%)	356 (94.9)	114 (94.2)	82 (96.5)	95 (91.3)	20 (100)	45 (100)	n.s.
<b>Cognitive functioning</b>							
Processing speed (sec), M (P)	45 (40–51)	43 (38–47)	43 (39–48)	46 (42–52)	55 (43–69)	61 (52–68)	A<C,D,E; B<C,D,E; C<D,E
Interference, M (P)	121 (92–160)	111 (87–140)	110 (92–136)	136 (100–213)	205 (123–260)	132 (107–200)	A<C,D,E; B<C,D,E
Working memory, M (P)	13 (11–16)	15 (13–17)	14 (12–16)	12 (11–14)	12 (10–14)	10 (9–12)	A>C,D,E; B>C,E; C>D,E
Immediate memory, M (P)	32 (26–37)	37 (33–40)	36 (33–38)	26 (23–29)	29 (23–34)	24 (20–28)	A>C,D,E; B>C,D,E; C<D,E
Delayed recall, M (P)	6 (4–8)	7 (6–8)	7 (6–8.5)	4 (3–5)	5 (3–5)	5 (3–6)	A>C,D,E; B>C,D,E
<b>Physical functioning</b>							
Gait speed (s), M (P)	6 (5–8)	6 (5–7)	6 (5–7)	6 (6–8)	20 (18–23)	9 (7–11)	A<C,E; B<C,D,E; C<D,E; D>E
Handgrip strength (kg), M (P)	26 (20–34)	28 (23–34)	28 (21–36)	25 (20–34)	17 (14–21)	20 (16–30)	A>E; B>D,E
Number of chronic diseases, M (P)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–2)	3 (1–4)	3 (1–3)	A<D,E; C<D,E

Notes: M = median; P = percentiles 25%–75%; IDS-SR = Inventory of Depressive Symptoms–Self-Report scale; LPA = latent profile analysis; n.s. = nonsignificant; Kruskal–Wallis test, Pearson chi-square.  
\*The *p*-values of the overall tests (Kruskal–Wallis or Pearson’s chi-square) were all <.001, except for female sex ( $\chi^2 = 10.0$ , *df* = 4, *p* = .04) and major depression ( $\chi^2 = 6.8$ , *df* = 4, *p* = .147).

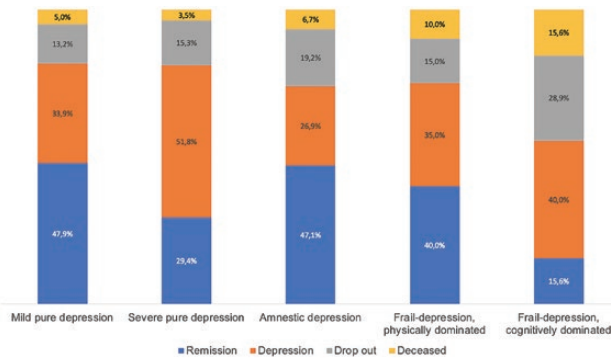


Figure 2. Outcome at 2-y follow-up.

severe pure depressed class ( $t = -5.2$ ,  $df = 301.5$ ,  $p < .001$ ) showed larger improvement of the IDS-SR scores. Compared with the severe pure depressed class, only the mild pure depressed class ( $t = 5.6$ ,  $df = 397.9$ ,  $p < .001$ ) and the amnestic depressed class ( $t = 4.87$ ,  $df = 410.5$ ,  $p < .001$ ) showed significantly less improvement of the IDS-SR scores (but remained lower).

### Change of Profile Parameters Over Time—Cognitive and Frailty Parameters

Repeated-measures ANOVAs adjusted for covariates identified a significant interaction term between LPA class membership and time for the dependent cognitive variables: interference score ( $F(4,242) = 2.44$ ,  $p = .048$ ), immediate memory score ( $F(4,245) = 6.49$ ,  $p < .001$ ), and delayed recall ( $F(4,246) = 3.97$ ,  $p = .004$ ), but not for processing speed ( $F(4,247) = 1.36$ ,  $p = .248$ ) and working memory ( $F(4,235) = 1.63$ ,  $p = .166$ ). With respect to the physical frailty parameters, we found a significant interaction between LPA class membership and time for gait speed ( $F(4,251) = 4.72$ ,  $p = .001$ ), but not for handgrip strength ( $F(4,253) = 2.44$ ,  $p = .913$ ). Table 3 presents the difference of the adjusted mean between baseline and follow-up for cognitive and frailty parameters.

Post hoc analyses comparing the late-life-related subtypes to both pure depressed subtypes yielded the following results.

Among patients in the amnestic class, the trajectory of immediate memory and delayed recall differed over time compared to patients in either the mild pure depressed class ( $F(1) = 24.3$ ,  $p < .001$  and  $F(1) = 13.2$ ,  $p < .001$ , respectively) or the severe pure depressed class ( $F(1) = 13.1$ ,  $p < .001$  and  $F(1) = 3.76$ ,  $p = .055$ , respectively). This was explained by a deterioration of immediate memory and of the delayed recall in both pure depressed classes.

Patients in the frail-depressed, physically dominated class improved significantly more over time with regard to interference control and gait speed compared with both the mild pure depressed class ( $F(1) = 5.67$ ,  $p = .019$  and  $F(1) = 14.0$ ,  $p < .001$ , respectively) and the severe pure depressed class ( $F(1) = 8.24$ ,  $p = .006$  and  $F(1) = 14.0$ ,  $p < .001$ , respectively). The absolute level of interference control and gait speed, however, remained worse at 2-year follow-up compared with both pure depressed classes.

The trajectory of immediate memory and delayed recall differed over time among patients in the frail-depressed, cognitively dominated class compared with patient in either the mild pure depressed class ( $F(1) = 6.46$ ,  $p = .012$  and  $F(1) = 4.81$ ,  $p = .031$ , respectively) or the severe pure depressed class ( $F(1) = 2.86$ ,  $p = .095$  and  $F(1) = 4.07$ ,  $p = .047$ , respectively). This was explained by a deterioration of immediate memory and of the delayed recall in both pure depressed classes.

### Sensitivity Analyses

Excluding the 23/375 (6.1%) patients scoring less than 25 on the MMSE did not change any of the analyses substantially (see Supplementary Material).

## Discussion

### Main Findings

Based on data-driven statistical techniques, we could distinguish five subgroups of depressed older patients differentiated by their scores on five cognitive domains, two physical frailty proxies, and three depressive symptoms dimensions. These subgroups could be labeled as (i) mild pure depression, (ii) severe pure depression, (iii) amnestic depression, (iv) frail-depression, cognitively dominated, and (v) frail-depression, physically dominated. The two subgroups with minimal signs of senescence (relatively good cognitive performance and low physical frailty) constituted over half of our sample (206/375, 54.9%). These two subgroups may represent two “pure depression” subtypes, which differed only with respect to depressive symptom severity. Depressive symptom severity improved significantly more among severely compared with mildly depressed older patients (perhaps due to more room for improvement). In line with previous studies (40), severely depressed patients still had a lower odds of remission at 2-year follow-up compared with mildly depressed patients.

The three nonpure depressed groups could be characterized by specific profile of cognitive deficits (verbal memory vs global cognitive impairment) and by the severity of physical frailty (normal vs low vs extreme low gait speed). Patients in these three subgroups were older (median 70–79 years) compared with those in the “pure depression” classes (median 65–68 years). Although not directly tested, it can be hypothesized that these subgroups are also characterized by higher levels of molecular and cellular senescence.

### The Subgroup of Amnestic Depression

The subgroup of patients labeled as “amnestic depression” had an isolated, worse performance on verbal memory, mild depressive symptom severity, and relatively good prognosis (remission in one of two patients and a low mortality rate). This clinical characterization fits with several hypotheses to explain the association between depression and dementia, including (i) depression as a prodrome of dementia, (ii) a state effect of depression on cognitive performance that lowers the threshold for manifesting dementia, (iii) depression as a causative factor for cognitive decline, for example, due to hippocampal damage through a glucocorticoid cascade, (iv) depression as an exacerbator of dementia, (v) depression as a reaction to cognitive deficits, and finally (vi) depression as a symptom of a related risk factor, such as cerebrovascular disease (41,42). In our subgroup “amnestic depression,” the memory impairment remained stable over a 2-year course, despite a high depression remission rate. Consequently, a state effect of depression on verbal memory is less likely. Furthermore, memory impairment remains relatively stable over a 2-year course in the preclinical phase of dementia (ie, amnestic mild cognitive impairment [aMCI]). Taken together, this subgroup of amnestic depression may therefore represent a subtype that is in the preclinical phase of dementia (43). An extended follow-up would have been interesting to validate this subtype as Alzheimer’s-related depression.

**Table 3.** Comparison of Mean (SE) of Baseline and Follow-up Data With Respect to Cognitive and Frailty Parameters of Patients With Data at Follow-up ( $n = 285$ ) Adjusted for Covariates

LPA Classes	Cognitive Parameters				Frailty Parameters			
	Processing Speed (s) <sup>a</sup>	Interference Control <sup>a</sup>	Working Memory	Immediate Memory	Delayed Recall	Gait Speed (s) <sup>a</sup>	Handgrip Strength (kg)	
Mild pure depression	Baseline (B)	115.8 (6.0)	14.9 (0.3)	36.7 (0.5)	7.3 (.2)	5.6 (0.5)	30.5 (0.9)	
	Follow-up (FU)	117.2 (6.1)	14.3 (0.3)	33.3 (0.6)	6.3 (.2)	6.2 (0.6)	28.7 (0.8)	
	Difference B-FU	1.4	-0.6	-3.4	-1.0	0.6	-1.8	
Severe pure depression	Baseline (B)	116.0 (7.6)	13.8 (0.4)	36.1 (0.6)	7.1 (0.2)	5.9 (0.2)	29.3 (1.1)	
	Follow-up (FU)	118.8 (7.7)	13.6 (0.4)	33.4 (0.8)	6.5 (0.3)	6.7 (0.2)	27.6 (1.0)	
	Difference B-FU	-0.02	-0.2	-2.7	-0.6	0.8	-1.7	
Amnesic depression	Baseline (B)	142.1 (8.1)	12.5 (0.4)	26.3 (.5)	4.3 (0.2)	6.4 (0.2)	27.4 (1.0)	
	Follow-up (FU)	124.2 (7.5)	12.9 (0.4)	27.6 (.7)	4.4 (0.2)	6.7 (0.2)	26.3 (0.9)	
	Difference B-FU	-17.9	0.4	1.3*#	0.1*	0.3	-1.1	
Frail-depression, physically dominated	Baseline (B)	181.1 (26.4)	13.3 (1.1)	29.6 (1.5)	5.2 (0.6)	12.7 (2.4)	24.1 (2.5)	
	Follow-up (FU)	111.6 (18.6)	12.7 (1.0)	29.3 (2.1)	5.2 (0.7)	8.4 (1.0)	23.8 (2.2)	
	Difference B-FU	69.5*#	-0.6	-0.3	0	-4.3*#	-0.3	
Frail-depression, cognitively dominated	Baseline (B)	135.4 (15.0)	10.0 (0.7)	24.4 (1.0)	4.4 (0.4)	7.6 (0.5)	26.6 (1.9)	
	Follow-up (FU)	119.5 (13.9)	9.9 (0.7)	25.0 (1.4)	4.9 (0.5)	7.7 (0.6)	26.4 (1.6)	
	Difference B-FU	-15.9	-0.1	0.6*	0.5*#	0.1	-0.2	

Notes: <sup>a</sup>Analyses were conducted on transformed parameters to reach a normal distribution (1/s for processing speed,  $\ln(-1 \times (\text{interference control} + 50))$  for interference control, and finally 1/s for gait speed). Presented values are back-transformed values for proper interpretation.

\* $p < .05$  for the difference between baseline and follow-up compared with the pure mild depressed class.

# $p < .05$  for the difference between baseline and follow-up compared with the pure severe depressed class.



### The Two Frail-Depressed Subgroups

The other two subgroups characterized by aging-related physical frailty and cognitive impairment were severely depressed, had a more global cognitive impairment, and had a slow gait speed. These both frail-depressed subgroups consisted of 17.3% (65/375) of the patients. This is consistent with prior research that observed the presence of frailty in 18%–25% of older adults with a DSM-IV defined depressive disorder (11,44). The co-occurrence of cognitive deficits and physical frailty, as found in our study, is in line with studies that recognize cognitive impairment as a component of frailty (45,46). This combination has been conceptualized as “cognitive frailty” by the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics (47). Mild cognitive deficits in memory, processing speed and executive functioning, however, are also common in late-life depression (48). Efforts to delineate specific subtypes of late-life depression related to cognitive impairment, no dementia (CIND) have resulted in the concepts of vascular depression and the depression-executive dysfunction syndrome (27,28). Vascular depression, depression presumed to be caused by underlying (cerebro)vascular disease, has been characterized by cognitive impairment in multiple domains. Whereas studies have shown that especially changes in processing speed may mediate performance in other cognitive domains (49,50), others argue that executive dysfunctioning is the main cognitive deficit in vascular depression (51). This latter notion has evolved to the concept of the depression-executive dysfunctioning syndrome (27,28), leaving room for other pathophysiological mechanisms in addition to vascular pathways. These patients are characterized by prominent frontostriatal dysfunction (23) and a poor response to antidepressants (23,27,28). A recent attempt to delineate subtypes of late-life depression based on their cognitive profile has resulted in two classes, that is, one subgroup with and one subgroup without cognitive impairment (52). Thus far, studies exploring the neuropsychological profile of patients suffering from late-life depression did not take physical frailty into account. A systematic review on the triad “depressed mood—executive dysfunction—slow gait,” however, found some evidence for vascular risk factors as a shared pathophysiological mechanism (53). Both frail-depressed subgroups we identified could be differentiated by their level of slowed gait speed. Gait speed is considered one of the best proxies for physical frailty and strongly associated with mortality (54). It should be distinguished from slowed thinking (processing speed) as slowed gait speed and processing speed differentially predict adverse health outcome such as cognitive decline, falls, and mortality, which point to separate underlying pathologies (55). Moreover, our prospective analyses showed that both frail-depressed subgroups also showed a differential course with respect to gait speed and interference control as well as had different remission and dropout rates.

Among patients in the frail-depressed, physically dominated subgroup, gait speed (and interference control) significantly improved over time, and the depression remission rate was relatively good (two of five patients). Moreover, patients in this subgroup were by far the oldest (see Table 2). This subgroup might represent a subgroup of frail patients in which the depressive disorder had an additional state effect on the frailty parameters (pseudofrailty). In other words, the extreme slowed gait speed and worse interference control of this subgroup might have been partly confounded by depression, for example, due to motivational problems. Nonetheless, at follow-up, these patients still performed worst compared with all other subgroups.

The frail-depressed, cognitively dominated subgroup had the lowest remission rate (one of six patients); significantly worse compared with the subgroup of mild pure depression (one of two), but not significantly worse compared with the subgroup of severe pure depression (one of three). This subgroup had the highest mortality. Moreover, cognitive deficits and slowed gait speed did not improve during follow-up in this subgroup.

The overlap between criteria for a depressive disorder and those for cognitive disorders and frailty (56,57) also raises the possibility that depressive symptomatology concurrent with frailty and/or cognitive deficits may not necessarily reflect “true” depression, but rather underlying age-related health conditions that may, for example, cause undue fatigue, sleep disturbances, or disinterest in pleasurable activities (58,59). This hypothesis offers an explanation for the high mortality rate and low remission rate in the frail-depressed, cognitively dominated group. Confounding of depressive symptom severity by underlying medical diseases has been demonstrated before. For example, in cardiac patients, the somatic-affective symptoms, but not cognitive-affective symptoms of depression are associated with cardiac disease severity and cardiac prognosis (30,60). These symptoms or symptom dimensions might simply reflect the severity of the underlying disease process.

### Methodological Considerations

This is the first longitudinal study to explore the existence of subtypes of depressive disorder characterized by aging-related features in older depressed persons. A strength of this study is that we included only patients with a depressive disorder according to DSM-IV-TR criteria instead of self-report depression rating scales. There are also some limitations of the present study.

First, causal interpretation is limited as subtyping was entirely based on cross-sectional baseline data. We had no data on the temporal order of depression, physical frailty, and cognitive impairment before baseline. Second, as subtyping by LPAs is based on group averages of phenotypic features, patients within the same class may still be heterogeneous with respect to their underlying etiology. Therefore, future studies should preferably include the assessment of senescence at the molecular, cellular, tissue, and system level. Third, we compared three subtypes characterized by age-related physical and cognitive features with both pure depressed subgroups. On the one hand, the depressive symptom severity of the frail-depressed groups is comparable to the severe pure depressed subgroup, which justify a comparison with this subgroup. On the other hand, comparison with the mild pure depressed subgroup seems relevant as physical frailty and cognitive impairment may result in falsely inflated self-report depressive symptom scores. Therefore, the best reference group might be in the middle.

Finally, to facilitate interpretation of the different late-life-related subtypes of depression, we evaluated the course of depression as well as the change of the clinical aging features prospectively. Nonetheless, selective dropout and mortality may have biased these results. Persons with missing data on follow-up had worse baseline scores of processing speed, working memory, verbal memory, and handgrip strength. The total dropout rates varied between 18% and 45%, with the highest dropout rates among subtypes characterized by cognitive decline with or without physical frailty. Because cognitive impairment and physical frailty are predictors of a worse course of a depressive disorder (17,24,61), selective dropout has probably attenuated the differences we found with respect to depression outcome.

## Conclusions/Clinical Implications

Depression is associated with accelerated aging. We found that more than half of the patients, that is 206/375 (55%), suffer from a “pure” depressive disorder with minimal age-related physical frailty and cognitive decline. The other 45% of our sample consisted of three subgroups that were characterized by age-related cognitive decline and physical frailty. These latter subtypes would be of interest for fundamental studies on senescence in late-life depression. From a clinical perspective, it would be relevant to examine whether and which subgroups might benefit from geriatric rehabilitation to reverse frailty or prevent its negative health outcomes (62,63) as well as psychotherapy to alleviate the negative psychological aspects of becoming and/or being frail (64). Nonetheless, as these assumptions have far-reaching consequences, randomized controlled studies are warranted stratified by age-related physical frailty and cognitive features.

## Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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## Conflict of Interest

None reported.

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