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Frailty as a Predictor of the Incidence and Course of Depressed Mood

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Abstract

Background—Late-life depression and physical frailty are supposed to be reciprocally associated, however, longitudinal studies are lacking.

Objectives—This study examines whether physical frailty predicts a higher incidence of depression, as well as a less favorable course of depression.

Methods—A population-based cohort study of 888 people aged 65 years and over with follow-up measures at 3, 6, and 9 years. Cox proportional hazards models adjusted for age, sex, education, smoking, alcohol usage, and global cognitive functioning were applied to calculate the incidence of depressed mood in those nondepressed at baseline (n = 699) and remission in those with depressed mood at baseline (n = 189). Depressed mood onset or remission was defined as crossing the cut-off score of 20 points on the Center for Epidemiological Studies-Depression Scale combined with a relevant change in this score. Physical frailty was based on the presence of ≥3 out of 5 components (ie, weight loss, weakness, slowness, exhaustion, and low physical activity level).

Results—A total of 214 out of 699 (30.6%) nondepressed persons developed depressed mood during follow-up. Physical frailty predicted the onset of depressed mood with a hazard rate of 1.26 (95% confidence interval 1.09–1.45, $P = .002$). Of the 189 persons with depressed mood at baseline, 96 (50.8%) experienced remission during follow-up. Remission was less likely in the presence of a higher level of physical frailty (hazard rate = 0.72, 95% confidence interval 0.58–0.91, $P = .005$).

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Conclusions—Because physical frailty predicts both the onset and course of late-life depressed mood, physical frailty should receive more attention in mental health care planning for older persons as well as its interference with treatment. Future studies into the pathophysiological mechanisms may guide the development of new treatment opportunities for these vulnerable patients.

Keywords

Depression; frailty; older persons; InCHIANTI

Late-life depression places a great burden on patients and society,[1] partly because of its often chronic course and high relapse rates.[2–5] Not only depressive disorder, but also clinically relevant depressive symptoms have high impact on well-being, disability, and utilization of health care services.[1] Late-life depression is a complex mood disorder with various etiological pathways and high comorbidity rates with cognitive decline and physical diseases.[6–9] These high comorbidity rates suggest involvement of general aging mechanisms. In an earlier study, we showed that 27% of depressed older patients can be classified as physically frail.[10] Recently, a consensus conference concluded that physical frailty is an important medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death.[11] Promising ideas were the optimism about the possibility to prevent and treat frailty and, thus, the need to take frailty into account in geriatric medicine.

Despite shared underlying pathophysiological mechanisms of depression and frailty,[12] the concept of frailty has received little attention in mental health care for older persons. This can partly be explained by overlapping criteria of frailty and psychiatric diseases, which is most apparent for broader frailty concepts (including both physical and psychosocial components, such as depressive symptoms). The physical frailty phenotype for example remained significantly associated with late-life depression when overlapping criteria were omitted.[13] Accordingly, latent class analyses have shown that physical frailty and depression identify distinct, but overlapping subpopulations.[14] For research into the relations between depression and frailty, the physical frailty phenotype by Fried et al,[15] defined as the presence of ≥3 out of the following 5 criteria: weight loss, weakness, slowness, exhaustion, and low physical activity level, is particularly useful, as depressive symptomatology is not part of this frailty definition. This is in line with the conclusions from the earlier mentioned consensus conference.[11]

If frailty indeed can be distinguished from late-life depression, it may be expected that physical frailty will be predictive for the onset of depression (as an adverse health effect). Additionally, it may be expected that frailty in depression is associated with negative health effects independent of the adverse effects of late-life depression itself, such as a more persistent course. Such data will contribute to the relevance of physical frailty in late-life mental health, and may ultimately lead to different interventions for frail and nonfrail persons, as previously have been suggested in general medicine.[16,17] To date, the impact of physical frailty on incident depression has been examined twice using a prospective study

design. Both studies identified physical frailty as an independent predictor of incident depression.[18,19] Generalization to a Western society, however, may be limited as both studies were conducted in an Asian population. Moreover, one of them had a follow-up duration limited to 15 months.[19]

The objectives of the present study are, therefore, to investigate whether in a Western society, physical frailty also predicts a higher incidence of depressed mood in nondepressed community-dwelling older persons and, whether physical frailty decreases the chance on remission of depressed mood in persons with depressed mood at baseline.

Methods

Data are from the InCHIANTI (Invecchiare in Chianti, aging in the Chianti area) Study, a prospective, population-based cohort study. Details of the study are described elsewhere.[20] Briefly, the baseline data collection started in 1998 and was completed in 2000. It included an interview at the homes of the participants and a medical examination at the study clinic. The medical examination was conducted within 21 days after the home interview. Follow-up assessments took place at 3, 6, and 9 years after baseline. After explaining the study procedures to the participants, they were asked to sign informed consent forms. The ethics committee of the Italian National Institute of Research and Care on Aging approved the study protocol.

The InCHIANTI study included 1155 persons aged 65 years and older. Because of the missing data on depressed mood at baseline (N = 76) or lack of follow-up data with respect to depressive symptoms (N = 191), the present study included 888 participants. Persons with missing data were significantly older [82.3 (standard deviation 7.6) vs 73.4 (6.3) years, $P < .001$], less educated [4.2 (3.2) vs 5.6 (3.3) years, $P < .001$], had more somatic diseases (1.18 vs 0.89, $P = .002$), and were more likely to be frail (20.2 vs 6.8%, $P < .001$). The 2 groups did not differ with respect to gender and depressed mood status at baseline.

Depressed Mood

Depressive symptoms were assessed at baseline, 3 years, 6 years, and 9 years of follow-up, using the Center for Epidemiological Studies-Depression Scale (CES-D). The CES-D is a self-report 20-item measurement scale for depressive symptoms experienced during the previous week.[21] It has been shown to be a valid and reliable instrument for identifying depressed mood in community-dwelling older adults.[22]

The sum score ranges from 0 through 60, whereas a score of 20 was the best indicator of clinically relevant depressive symptoms within the InCHIANTI sample.[23,24] Crossing the cut-off of 20 points combined with a relevant change on the CES-D was considered the primary outcome variable (ie, onset of depressed mood in case of no depressed mood at baseline and remitted depressed mood in case of depressed mood at baseline). A relevant change was defined as a decrease or an increase of at least 4 points (one-half a standard deviation) on the CES-D between 2 measurements. This criterion of a minimum change of 4 points was chosen to avoid random fluctuations or clinically irrelevant changes of symptoms

leading to a respondent being identified as either incident depressed or remitted from depressed mood.

Frailty

Frailty was defined according to the widely used criteria of Fried et al.[15] In this definition, frailty is operationalized as the presence of ≥3 out of the following 5 criteria: weight loss, weakness, slowness, exhaustion, and low physical activity level. In the analyses, however, frailty was used as a continuous variable based on the number of criteria met (range 0–5). Each criterion was operationalized using previously published methods.[25,26]

- Weight loss was defined as the unintentional weight loss of > 4.5 kg in the past year.
- Handgrip strength was used to assess weakness. If handgrip strength corresponded to the lowest quintile for stratified gender and body mass index groups, weakness was considered present.
- Slowness was measured by a 4-m walking test and was considered to be present when walking speed corresponded to the lowest quintile of stratified gender and height groups.
- Exhaustion was evaluated by a CES-D question (“How often in the last week did you feel that everything you did was an effort?”). If the participants answered “often” or “most of the time,” exhaustion was considered present.
- Low physical activity was assessed during the home interview. It was defined as sedentary state or performing light intensity activity (ie, walking) less than 1 hour a week.

Covariates

The following covariates were included in the analyses: socio-demographic variables, life style variables, and cognitive functioning. Sociodemographic variables included age, gender, and years of education. Life style variables included smoking (nonsmoker/former smoker/current smoker) and alcohol use (<3 or ≥3 drinks a day). Cognitive functioning was measured by the Mini-Mental State Examination (MMSE).[27]

The number of somatic diseases was established using standardized criteria that combined information from self-report history, medical records, and a clinical examination (including heart failure, coronary heart disease, stroke, chronic obstructive lung disease, hypertension, diabetes, cancer, Parkinson disease, and hip arthritis).

Statistical Analyses

All analyses will be presented for persons with depressed mood (CESD score ≥20) and nondepressed (CESD score <20) persons at baseline. Demographics and clinical characteristics of the participants with and without frailty (yes/no) were compared using independent samples *t* tests for normally distributed, continuous variables, nonparametric Mann-Whitney U tests for skewed continuous variables, and χ^2 tests for categorical

variables. All predictors and covariates (primary variables) that were included in the models were checked for normality and collinearity.

Missing data of determinants and covariates were handled by multiple imputations using the fully conditional specification method with IBM SPSS statistics (SPSS Inc, Chicago, IL), whereas the outcomes (depressed mood status) were not. Appendix 1 and 2 show the variables in the imputation model and their role in the model (predictor, imputed variable, or both).

In the nondepressed group, 43 datasets were created because 43% of the cases had missing data on at least 1 variable. In the depressed mood group, 58 datasets were created.[28] Analyses on the imputed dataset were considered the primary analyses. Nonetheless, results of the original data (complete cases) were also shown.[28,29]

Cox proportional hazards models adjusted for age, gender, education, smoking status, alcohol use, and MMSE score were used to examine whether frailty predicts incidence of depressed mood during follow-up (either at 3, 6, or 9 years of follow-up, CES-D scores of ≥20 combined with a relevant change)[24] among those originally not depressed at enrollment. The proportionality of hazards assumption was checked for the primary variables by log minus log plots.

Only subjects with data from at least 1 follow-up measure were included in the analysis. First, the number of frailty components (range 0–5) was used as a continuous predictor variable. Subsequently, the impact of the individual frailty components was examined by including each component in a separate model.

Among persons with depressed mood at baseline, a similar strategy was applied. We used Cox proportional hazards models to examine whether frailty status at baseline predicted remission of depressed mood during follow-up.

Interactions with gender were tested because the prevalence rates for both frailty and depression are higher in women than in men. Finally, because the exhaustion criterion from the physical frailty definition is derived from a depression scale (CES-D), we performed sensitivity analysis by excluding the exhaustion criterion from the frailty definition. The sum score was re-calculated on the remaining 4 frailty components. With this measure of frailty, the analyses were repeated. All statistical procedures were performed using IBM SPSS v 20. Final outcomes were considered statistically significant if P values were ≤.05.

Results

The mean age (standard deviation) of total study population (n =888) 73.4 (6.3) years and 56.3% was female. At baseline, 21.3% had depressed mood, and 6.8% were frail. Table 1 presents the characteristics of both the depressed mood and the nondepressed group by frailty status.

Persons with baseline depressed mood were significantly older, were more often female, were less frequently a smoker, drank less alcohol, had lower cognitive functioning, were more likely to be frail, and were more likely to have depressed mood at follow-up.

Incidence of Depressed Mood

Incidence of depressed mood was assessed in persons who were not depressed at baseline (n = 699). Of these persons 92.4% (n = 646) had CES-D data available at 3 years of follow-up, 81.4% (n = 569) at 6 years follow-up, and 64.2% (n = 449) at 9 years follow-up. Of the persons not depressed at baseline, 30.6% (n = 214) developed depressed mood during the 9-year follow-up. The risk of becoming depressed was increased for persons with frailty, compared with the nonfrail persons in the unadjusted analyses. When the analyses were corrected for age, gender, educational level, smoking status, alcohol use, number of somatic diseases, and MMSE score, this increased risk remained present [hazard rate (HR) = 1.26, 95% confidence interval (CI) 1.09–1.45, $P = .002$]. Subsequently, frailty components were analyzed separately. Only low physical activity level significantly increased the risk of incident depressed mood (Table 2).

Remission in Depressed Mood Group

Remission of depressed mood was assessed in persons who had depressed mood at baseline (n = 189). Follow-up data were available for 93.7% (n = 177) at 3 years follow-up, for 73.0% (n = 138) at 6 years follow-up, and for 49.7% (n = 94) at 9 years follow-up. Of the persons with initially depressed mood, 50.8% (n = 96) experienced remission during follow-up.

With regard to remission during follow-up, Cox regression analysis showed that frailty strongly predicts lower remission during follow-up (Table 3). This increased likelihood of remission remained present, also in the fully adjusted model (HR = 0.72, 95% CI 0.58–0.91, $P = .005$). When frailty was decomposed into components, only absence of low physical activity level predicted remission of depressed mood in the fully adjusted model (Table 3). No significant interactions between frailty and gender were found (nondepressed mood group: $P = .919$, depressed mood group: $P = .621$).

Sensitivity Analysis

The analyses were repeated after excluding the exhaustion criterion from the frailty definition. Frailty without exhaustion remained significantly associated with incident depressed mood and remission in the fully adjusted model (incidence: HR = 1.31, 95% CI 1.10, 1.56, $P = .003$, remission: HR = 0.70, 95% CI 0.53, 0.92, $P = .010$).

Discussion

Main Findings

This study describes the longitudinal association between physical frailty and depressed mood; focusing on incidence as well as remission of depressed mood. It is confirmed that the severity of frailty negatively interferes with both the onset and remission of late-life

depressed mood independent of age, sex, level of education, lifestyle, somatic diseases, and global cognitive functioning.

Comparison With Literature

Our findings are fully in line with a recent systematic review on the relationship between frailty and depression.[30] The authors concluded that frailty, its components, and functional impairments are risk factors for depression.[30] In most of the included cohort studies, however, frailty was defined by Activities of Daily Living indices. None of these cohort studies used a definition of frailty according to the physical phenotype. This is important, as physical frailty should reflect the biological age of a person and should be distinguished from disabilities and multimorbidity.[11] Not included in this review are 2 recent studies on the longitudinal association between physical frailty and depression.[18,19] Both studies find that physical frailty predicts the incidence of depressive symptoms in an Asian population. In 1 study, the persistence of depressive symptoms is also investigated, and frailty is identified as an independent predictor of persistence of depressive symptoms.[18] Our findings not only confirm these findings for a Western population, but also extend these findings by determining the contribution of frailty to remission in a group that has depressed mood at baseline. Furthermore, the risk of depression in the case of frailty is also confirmed for a relatively long follow-up period (9 years).

With regard to components of frailty; weight loss, slowness, exhaustion, and low physical activity seem to contribute to the impact of frailty on the onset of depressed mood, whereas the impact of weakness seems to be less strong. Nonetheless, only low physical activity significantly increased the risk of depressed mood onset in the fully adjusted models. The association between low physical activity and incident depression is in line with previous studies.[31]

Among older persons suffering from depressed mood, frailty was associated with a lower chance on remission during follow-up. The impact of frailty on remission of depressed mood seems to be driven by slowness and low physical activity level, whereas an impact of and weight loss was reverse. Previous research showed the same (nonsignificant) inverse association of weight loss with depressed mood.[18] Nonetheless, again only (absence of) low physical activity level was an independent predictor of remission in the fully adjusted models.

So, what do the findings among depressed and nondepressed persons tell us about the concept of frailty? The physical frailty phenotype according to the criteria of Fried et al[15] is a widely used and well-validated concept.[11] In our study, the construct of frailty is consistently associated with depressed mood. Results with respect to the individual frailty components also seem consistent. With respect to the prediction of depressed mood, all components pointed toward the same direction. Regarding remission of depressed mood, the association with weight loss is opposite to the direction of the association of the other frailty components. When the uni-dimensionality of physical frailty is examined with respect to its association with late-life depression, zooming in on frailty components may help revealing the validity of the concept of frailty. Future studies, therefore, should pay more attention to the relationship between adverse outcomes and the individual components of frailty.

In recent research, it was found that overlap between depression and frailty was highest for the somatic and severely depressed subgroups; almost three-quarters of the severely depressed older persons was also frail.[32] The co-occurrence of frailty and depressed mood is confirmed in the present study. The frailty prevalence of 6.8% in the present study, however, is lower than the prevalence rate we found before in a meta-analysis of frailty prevalence among community dwelling older persons (10.7%).[10] This difference can almost completely be explained by the higher prevalence of frailty (20.2%) among the persons that were excluded due to missing data. Nonetheless, another less weighty explanation for this finding may be the lower age of the InCHIANTI participants, compared with the mean age of the participants in the meta-analysis, as the prevalence of frailty increases with age.

What underlies this compound between physical frailty and depression? Shared mechanisms include low-graded inflammation, nutritional deficits among which vitamin D deficiency, lack of exercise and sarcopenia, and/or age-related hormonal changes, which all have been associated with frailty as well as depression.[31,33–40] These pathophysiological mechanisms add to the multifacetted pathways to both frailty and depression. Moreover, when depression and frailty are simultaneously present, disentangling causes and consequences of either one from another becomes challenging. For instance, a factor like lack of exercise can be part of the path toward frailty and depression, as well as a result of one or both of these syndromes. All factors may even occur in a complicated vicious circle. Nonetheless, the longitudinal association between frailty and depression is clearly present in this study. Therefore, treatment of frailty deserves a more prominent role in late-life depression, as it may prevent depression or shorten the duration of depression. Older persons that are not only depressed, but also frail confer specific complex care needs.[41,42]

Strengths and Limitations

Our study has some important strengths. The association between frailty and depressed mood was examined within a prospective design, with data of 9 years of follow-up. A large, community-based sample was used, providing the opportunity to investigate onset, as well as persistence of depressed mood. Frailty was included as a continuous variable, reflecting the dimensional nature of physical frailty.[43] Relations were further disentangled by examining components of frailty separately.

Because the dropout of study participants during follow-up is selective when studying older persons (in our case the most frail participants dropped out during follow-up, data not shown), the strength of the association between frailty and depressed mood may decrease at the end of the follow-up time (9 years). Cox regression analysis takes this into account by censoring the data at time of dropout. Nonetheless, the findings have to be interpreted in light of the study limitations also. In our sample, persons with missing data on baseline depressive symptoms or all follow-up data on depressive symptoms were excluded prior to the analyses. The persons with missing data were older, less educated, more frail, and had more somatic diseases, compared with persons with no missing data. This implies that the most frail and unhealthy persons were not included in the analyses, and, therefore, the findings may be biased toward an underestimation of the association between frailty and depressed mood.

Depressive symptoms were assessed with the CES-D; a self-report questionnaire. With a score of ≥20 combined with a relevant change in symptoms (≥4 CES-D points), a person was considered to have depressed mood. Although a CES-D score of 20 points or more reflects clinically relevant depressive symptoms,[22,44] it is not necessarily a psychiatric diagnosis of major depressive disorder.[22] Our results should, therefore, be confirmed by future studies assessing depressive disorder according to DSM-5 or International Classification of Diseases-10th revision criteria. Finally, the history of depression was unknown, and some of the persons in the nondepressed group may have suffered from depressed mood in the past.

Clinical Implications

This study confirms that frailty predicts incidence of depressed mood and not being frail predicts remission. In long-term care, both frailty and depression are highly prevalent,[45,46] and these findings may change the perspective on the treatment of late-life depression and frailty. Our results imply that interventions proven to improve the frailty status, such as exercise, nutritional intervention, and vitamin D supplementation,[11] might be relevant for old age psychiatry and for prevention of frailty. Future research should guide interventions for persons suffering from frailty and depression, especially the influence of treating frailty and the consequences for depression.

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References

1. Beekman AT, Penninx BW, Deeg DJ, et al. The impact of depression on the well-being, disability and use of services in older adults: A longitudinal perspective. Acta Psychiatr Scand. 2002; 105:20–27. [PubMed: 12086221]
2. Stek ML, Van Exel E, Van Tilburg W, et al. The prognosis of depression in old age: Outcome six to eight years after clinical treatment. Aging Ment Health. 2002; 6:282–285. [PubMed: 12217097]
3. Mueller TI, Kohn R, Leventhal N, et al. The course of depression in elderly patients. Am J Geriatr Psychiatry. 2004; 12:22–29. [PubMed: 14729555]
4. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: A systematic review of comparative studies. Am J Psychiatry. 2005; 162:1588–1601. [PubMed: 16135616]
5. Licht-Strunk E, van der Windt DA, van Marwijk HW, et al. The prognosis of depression in older patients in general practice and the community. A systematic review. Fam Pract. 2007; 24:168–180. [PubMed: 17237495]
6. Beekman AT, de Beurs E, van Balkom AJ, et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. Am J Psychiatry. 2000; 157:89–95. [PubMed: 10618018]
7. Lenze EJ, Rogers JC, Martire LM, et al. The association of late-life depression and anxiety with physical disability: A review of the literature and prospectus for future research. Am J Geriatr Psychiatry. 2001; 9:113–135. [PubMed: 11316616]
8. Steffens DC, McQuoid DR, Potter GG. Outcomes of older cognitively impaired individuals with current and past depression in the NCODE study. J Geriatr Psychiatry Neurol. 2009; 22:52–61. [PubMed: 19196631]

9. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health. 2013; 34:119–138. [PubMed: 23514317]
10. Collard RM, Boter H, Schoevers RA, et al. Prevalence of frailty in community-dwelling older persons: A systematic review. J Am Geriatr Soc. 2012; 60:1487–1492. [PubMed: 22881367]
11. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: A call to action. J Am Med Dir Assoc. 2013; 14:392–397. [PubMed: 23764209]
12. Révész D, Verhoeven JE, Milaneschi Y, et al. Dysregulated physiological stress systems and accelerated cellular aging. Neurobiol Aging. 2014; 35:1422–1430. [PubMed: 24439483]
13. Collard RM, Comijs HC, Naarding P, Oude Voshaar RC. Physical frailty: Vulnerability of patients suffering from late-life depression. Aging Ment Health. 2014; 18:570–578. [PubMed: 23998249]
14. Mezuk B, Lohman M, Dumenci L, Lapane KL. Are depression and frailty overlapping syndromes in mid- and late-life? A Latent Am J Geriatr Psychiatry. 2013; 21:560–569. [PubMed: 23567406]
15. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56:M146–M156. [PubMed: 11253156]
16. Afilalo J, Karunananthan S, Eisenberg MJ, et al. Role of frailty in patients with cardiovascular disease. Am J Cardiol. 2009; 103:1616–1621. [PubMed: 19463525]
17. Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: Understanding frailty and the geriatric assessment. CA Cancer J Clin. 2010; 60:120–132. [PubMed: 20173172]
18. Feng L, Nyunt MS, Yap KB, Ng TP. Frailty predicts new and persistent depressive symptoms among community-dwelling older adults: Findings from Singapore longitudinal aging study. J Am Med Dir Assoc. 2014; 15:76.e7–76.e12.
19. Makizako H, Shimada H, Doi T, et al. Physical frailty predicts incident depressive symptoms in elderly people: Prospective findings from the Obu Study of Health Promotion for the Elderly. J Am Med Dir Assoc. 2014 Oct 9. Epub ahead of print.
20. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems contributing to the decline in ability to walk: Bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. J Am Geriatr Soc. 2000; 48:1618–1625. [PubMed: 11129752]
21. Radloff L. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1:385–401.
22. Beekman AT, Deeg DJ, Van Limbeek J, et al. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): Results from a community-based sample of older subjects in The Netherlands. Psychol Med. 1997; 27:231–235. [PubMed: 9122304]
23. Vogelzangs N, Suthers K, Ferrucci L, et al. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. Psychoneuroendocrinology. 2007; 32:151–159. [PubMed: 17224244]
24. Penninx BW, Guralnik JM, Ferrucci L, et al. Depressive symptoms and physical decline in community-dwelling older persons. JAMA. 1998; 279:1720–1726. [PubMed: 9624025]
25. Ble A, Cherubini A, Volpato S, et al. Lower plasma vitamin E levels are associated with the frailty syndrome: The InCHIANTI study. J Gerontol A Biol Sci Med Sci. 2006; 61:278–283. [PubMed: 16567378]
26. Cesari M, Leeuwenburgh C, Lauretani F, et al. Frailty syndrome and skeletal muscle: Results from the Invecchiare in Chianti study. Am J Clin Nutr. 2006; 83:1142–1148. [PubMed: 16685058]
27. Folstein M, Folstein S, McHugh P. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
28. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. BMJ. 2009; 338:b2393. [PubMed: 19564179]
29. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011; 30:377–399. [PubMed: 21225900]
30. Mezuk B, Edwards L, Lohman M, et al. Depression and frailty in later life: A synthetic review. Int J Geriatr Psychiatry. 2012; 27:879–892. [PubMed: 21984056]
31. Wassink-Vossen S, Collard RM, Oude Voshaar RC, et al. Physical (in)activity and depression in older people. J Affect Disord. 2014; 161:65–72. [PubMed: 24751309]

32. Lohman M, Dumenci L, Mezuk B. Sex differences in the construct overlap of frailty and depression: Evidence from the health and retirement study. J Am Geriatr Soc. 2014; 62:500–505. [PubMed: 24576097]
33. Cesari M, Penninx B, Pahor M, et al. Inflammatory markers and physical performance in older persons: The InCHIANTI study. J Gerontol A Biol Sci Med Sci. 2004; 59:242–248. [PubMed: 15031308]
34. Leng SX, Xue QL, Tian J, et al. Inflammation and frailty in older women. J Am Geriatr Soc. 2007; 55:864–871. [PubMed: 17537086]
35. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. BMC Med. 2013; 11:129. [PubMed: 23672628]
36. Cesari M, Landi F, Vellas B, et al. Sarcopenia and physical frailty: Two sides of the same coin. Front Aging Neurosci. 2014; 6:192. [PubMed: 25120482]
37. Kim NH, Kim HS, Eun CR, et al. Depression is associated with sarcopenia, not central obesity, in elderly korean men. J Am Geriatr Soc. 2011; 59:2062–2068. [PubMed: 22092258]
38. Shardell M, Hicks GE, Miller RR, et al. Association of low vitamin D levels with the frailty syndrome in men and women. J Gerontol A Biol Sci Med Sci. 2009; 64:69–75. [PubMed: 19164273]
39. Milaneschi Y, Hoogendijk W, Lips P, et al. The association between low vitamin D and depressive disorders. Mol Psychiatry. 2014; 19:444–451. [PubMed: 23568194]
40. Savela SL, Koistinen P, Stenholm S, et al. Leisure-time physical activity in midlife is related to old age frailty. J Gerontol A Biol Sci Med Sci. 2013; 68:1433–1438. [PubMed: 23525478]
41. Han H, Kim M, Lee HB, et al. Correlates of depression in the Korean American elderly: Focusing on personal resources of social support. J Cross Cult Gerontol. 2007; 22:115–127. [PubMed: 17136454]
42. Wild B, Heider D, Maatouk I, et al. Significance and costs of complex bio-psychosocial health care needs in elderly people: Results of a population-based study. Psychosom Med. 2014; 76:497–502. [PubMed: 25121639]
43. Collard RM, Arts M, Comijs HC, et al. The role of frailty in the association between depression and somatic comorbidity: Results from baseline data of an ongoing prospective cohort study. Int J Nurs Stud. 2015; 52:188–196. [PubMed: 25443303]
44. Fava GA. Assessing depressive symptoms across cultures: Italian validation of the CES-D self-rating scale. J Clin Psychol. 1983; 39:249–251. [PubMed: 6841626]
45. de la Rica-Escuin M, Gonzalez-Vaca J, Varela-Perez R, et al. Frailty and mortality or incident disability in institutionalized older adults: The FINAL study. Maturitas. 2014; 78:329–334. [PubMed: 24929996]
46. Bruce ML, McAvay GJ, Raue PJ, et al. Major depression in elderly home health care patients. Am J Psychiatry. 2002; 159:1367–1374. [PubMed: 12153830]

Appendix 1. Missing Data Patterns in Persons With Depressed Mood at Baseline

Variable N = 189	N (%) Cases With Missing Values	Role
Age	0 (0)	Predictor
Gender	0 (0)	Predictor
Education	0 (0)	Predictor
Smoking status	0 (0)	Predictor
Alcohol use	0 (0)	Predictor
MMSE score	0 (0)	Predictor

Variable N = 189	N (%) Cases With Missing Values	Role
Somatic diseases	0 (0)	Predictor
Weight loss	8 (4.2)	Predictor and imputed
Grip strength	22 (11.6)	predictor and imputed
Walking speed	27 (14.3)	Predictor and imputed
Exhaustion	0 (0)	Predictor
Low activity level	0 (0)	Predictor
CES-D follow-up 1	12 (6.3)	Predictor
CES-D follow-up 2	51 (27.0)	Predictor
CES-D follow-up 3	95 (50.3)	Predictor
CES-D baseline	0 (0)	Predictor

When patterns of missing data were analyzed, it showed that data was missing by a random pattern and, therefore, the Fully Conditional Specification Method was used. We created 58 datasets, as 58% of the cases had at least 1 missing value.[29] In total, 7.1% of the data were missing. The imputation included the variables that were used in the final model.

Appendix 2. Missing Data Pattern in the Group Nondepressed at Baseline

Variable N = 699	N (%) Cases With Missing Values	Role
Age	0 (0)	Predictor
Gender	0 (0)	Predictor
Education	0 (0)	Predictor
Smoking status	0 (0)	Predictor
Alcohol use	0 (0)	Predictor
MMSE score	0 (0)	Predictor
Somatic diseases	0 (0)	Predictor
Weight loss	5 (0.7)	Predictor and imputed
Grip strength	35 (5.0)	predictor and imputed
Walking speed	48 (6.9)	predictor and imputed
Exhaustion	0 (0)	Predictor
Low activity level	0 (0)	Predictor
CES-D follow-up 1	53 (7.6)	Predictor
CES-D follow-up 2	130 (18.6)	Predictor
CES-D follow-up 3	250 (35.8)	Predictor
CES-D baseline	0 (0)	Predictor

When patterns of missing data were analyzed, it showed that data was missing by a random pattern and therefore the Fully Conditional Specification Method was used. We used the Fully Conditional Specification Method and created 43 datasets, as 43% of the cases had at least 1 missing value.[29] In total, 4.7% of the data were missing. The imputation included the variables that were used in the final model.

Table 1

Sample Characteristics (Complete Cases)

Characteristic	Participants (n = 888), %					
	Depressed Mood at Baseline (n = 189), 21.3		*P* Value*	No Depressed Mood at Baseline (n = 699), 78.7		*P* Value*
	Frail (n = 31), 16.4	Not Frail (n = 158), 83.6		Frail (n = 29), 4.1	Not Frail (n = 670), 95.9	
Sociodemographics						
Age, mean (SD), year	79.9 (6.2)	74.6 (6.4)	<.001	77.0 (7.1)	72.6 (6.0)	<.001
Female gender, %	77.4	77.8	.958	48.3	50.6	.807
Education, mean (SD), y	4.3 (2.7)	5.4 (3.4)	.072	5.4 (3.1)	5.7 (3.3)	.622
Health indicators						
Smoking, %			.560			.120
Never smoked	77.4	72.8		37.9	54.3	
Former smoker	9.7	17.1		34.5	30.4	
Current smoker	12.9	10.1		27.6	15.2	
Alcohol use, ≥3 drinks a day, %	3.2	12.0	.145	13.8	22.8	.253
MMSE score, mean (SD)	23.3 (2.9)	25.3 (2.8)	<.001	24.4 (3.4)	25.9 (2.7)	.023
Somatic diseases, mean no (SD)	1.4 (1.1)	0.9 (1.0)	.007	1.7 (1.2)	0.8 (0.9)	<.001
Frailty indicators						
Weight loss, %	25.8	3.8	<.001	27.6	3.1	<.001
Weakness, %	58.1	11.4	<.001	75.9	13.0	<.001
Slowness, %	80.6	16.4	<.001	86.2	10.9	<.001
Exhaustion, %	83.9	46.8	<.001	65.5	7.5	<.001
Low physical activity level, %	80.6	24.1	<.001	72.4	8.2	<.001
Amount of frailty criteria present, mean (SD)	3.3 (0.5)	1 (0.7)	<.001	3.3 (0.5)	0.4 (0.7)	<.001

SD, standard deviation.

*Comparison using analyses of variance (continuous variables), χ^2 statistics (categorical variables), and U tests (continuous, skewed variables).

Table 2

Cox Proportional Hazards Model for Incidence of Depressed Mood in the Group Not Depressed at Baseline[*]

N = 699	Imputed Data		Complete Cases	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Frailty (N = 29)[†]:				
Unadjusted	1.41 (1.24, 1.60)	<.001	1.43 (1.23, 1.60)	<.001
Fully adjusted[‡]	1.26 (1.09, 1.45)	.002	1.25 (1.08, 1.46)	.003
Components of frailty[‡]:				
Weight loss (N = 29)	1.49 (0.80, 2.76)	.205	1.48 (0.79, 2.75)	.218
Weakness (N = 115)	1.21 (0.85, 1.73)	.279	1.20 (0.84, 1.71)	.329
Slowness (N = 106)	1.39 (0.95, 2.03)	.087	1.36 (0.92, 2.02)	.123
Exhaustion (N = 69)	1.40 (0.95, 2.08)	.090	1.40 (0.95, 2.08)	.090
Low physical activity level (N = 76)	1.68 (1.17, 2.42)	.005	1.68 (1.17, 2.42)	.005

[*] Number of events: 214, number of person years: 4668 (45.8 events/1000 person years).

[†] Frailty was used as a continuous variable.

[‡] Frailty components were analyzed separately and adjusted for age, gender, level of education, smoking status, alcohol use, number of somatic diseases, and MMSE score.

Table 3

Cox Proportional Hazards Model for Remission in the Group Depressed Mood at Baseline *

N = 189	Imputed Data		Complete Cases	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Frailty (N = 31) †:				
Unadjusted	0.73 (0.60, 0.90)	.003	0.73 (0.59, 0.90)	.004
Model 1	0.72 (0.58, 0.91)	.005	0.74 (0.58, 0.93)	.010
Components of frailty ‡:				
Weight loss (N = 15)	1.17 (0.54, 2.50)	.688	1.22 (0.58, 2.57)	.600
Weakness (N = 41)	0.66 (0.35, 1.24)	.195	0.65 (0.34, 1.24)	.190
Slowness (N = 53)	0.55 (0.30, 1.01)	.052	0.55 (0.30, 1.02)	.057
Exhaustion (N = 100)	0.75 (0.49, 1.13)	.169	0.75 (0.49, 1.13)	.169
Low physical activity level (N = 63)	0.55 (0.33, 0.94)	.028	0.55 (0.33, 0.94)	.0.28

* Number of events: 96, number of person years: 999 (96.1 events/1000 person years).

† Frailty was used as a continuous variable.

‡ Frailty components were analyzed separately and adjusted for age, gender, level of education, smoking status, alcohol use, number of somatic diseases, and MMSE score.