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Frailty and depression in older adults: A high-risk clinical population

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Abstract

Objectives—To identify salient characteristics of frailty that increase risk of death in depressed elders.

Design—Data from the Nordic Research on Ageing Study.

Setting—Research sites in Denmark, Sweden, and Finland.

Participants—Sample included 1027 75-year-old adults, 436 men and 591 women.

Main Outcome Measure—Time of death was obtained, providing a maximum survival time of 11.08 years (initial evaluation took place between 1988-1991).

Results—Depressed elders showed greater baseline impairments in each frailty characteristic (gait speed, grip strength, physical activity levels, and fatigue). Simultaneous models including all four frailty characteristics showed slow gait speed (HR, 1.84; 95% CI, 1.05-3.21) and fatigue (HR, 1.94; 95% CI, 1.11-3.40) associated with faster progression to death in depressed women; none of the frailty characteristics in the simultaneous model were associated with death in depressed men. In women, the effect of impaired gait speed on mortality rates nearly doubled when depression

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was present (mortality rates, nondepressed women: no gait impairment =26%; slow gait =40%; depressed women: no gait impairment=32%; slow gait =58%). A similar pattern was observed for fatigue.

Conclusions—The confluence of specific characteristics of frailty (fatigue and slow gait speed) and depressive illness is associated with an increased risk of death in older adults; this association is particularly strong in older depressed women. Future research should investigate whether multimodal interventions targeting depressive illness, mobility deficits, and fatigue can decrease mortality and improve quality of life in older depressed individuals with characteristics of the syndrome of frailty.

Frailty is a syndrome defined by weakness, fatigue, low physical activity, slowed gait, and unintentional weight loss. These declines across multiple physiologic systems[1] develop incrementally with weakness emerging early in the process and weight loss and fatigue representing a final pathway towards frailty.[1-4] The syndrome, a clinical marker for disease and/or physiological decline, is associated with greater depressive symptoms and disability.[1, 5, 6] Frailty characteristics are prevalent in the community, with estimates of prefrailty (1-2 characteristics) or frailty (3+ characteristics) as high as 7% of community dwelling elders over the age of 65, and 18% of those over the age of 80. Three year follow-up data[2] showed that prefrail elders had more than a 3-fold higher risk of death compared with non-frail elders; frail elders had a 6-fold higher risk of death. Thus a significant proportion of community dwelling elderly are at a “tipping point” towards dire outcomes.

Depression is another disease prevalent in older adults associated with disability and increased mortality; It is estimated that 2.6% of community-dwelling elders suffer from a mood disorder, a rate believed to be an underestimation due to underdiagnosis, the presence of subthreshold symptoms, and a lack of high-risk older adults assessed.[7] The diagnosis and treatment of late life depression is complicated by increased risk of comorbid disability, medical disorders, and cognitive impairment.[8-15]

There is *phenomenological* overlap between late life depression and frailty, with symptoms common to both depression (weight loss, decreased physical activities, low energy) and frailty (fatigue, decreased leisure activities, weight loss).[16] The Cardiovascular Health Study[1] reported that the rate of depressive symptoms increased proportional to the number of frailty characteristics present.[1] Yet despite these associations, there has been little research focused on this high-risk clinical population.[16-21] Therefore, although characteristics of frailty have been predictive of mortality in nondepressed older adults, it is not known if these same characteristics are predictive in depressed elders or whether the presence of depression increases the risk of mortality in these individuals.

Using data from the Nordic Research on Ageing study (NORA[22-24]), we investigated the effect of the presence of frailty characteristics on mortality in older adults with differing degrees of depressive symptomatology. We hypothesized that in the depressed sample low grip strength and gait speed rather than fatigue and low physical activities (characteristics of frailty that overlap with symptoms of depression) would predict mortality.

Methods

Participants

The purpose of the NORA study was to determine the functional capacity of 75-year-olds from Glostrup in Denmark, Göteborg in Sweden, and Jyväskylä in Finland.[5, 22-24] Data were obtained in January 2012 for 1204 older adults who were 75 years of age at the time of evaluation (conducted between 1988 and 1991). The sample used in this study consisted of 1027 older adults. Participants were excluded because of missing baseline depression data or missing data on all of the four frailty characteristics.

Measures

FRAILTY CHARACTERISTICS

Individuals were coded as having a frailty characteristic if they scored in the bottom 25th percentile of the total sample of 1027 older adults on that particular assessment.[1, 2] Participants were coded as missing if they did not have a value on a frailty assessment. Missingness was coded for the survival analyses to investigate the potential meaning of missing data.

Grip strength—Handgrip strength was assessed in kilograms (kg) of force. Men with grip strength ≤ 36.71 kg and women ≤ 20.90 kg were coded as having the frailty characteristic of low grip strength. 173 of the 1027 were coded as missing.

Gait speed—Ten-meter walking time was coded as meters per second. Men with gait speed ≤ 1.43 m/s and women ≤ 1.25 m/s were coded as having the frailty characteristic of slow gait speed. 145 of the 1027 were coded as missing.

Fatigue—Fatigue was assessed by the Avlund Mob-T Scale that ranges from 0 to 6 with high scores denoting greater fatigue.[25] Participants who scored 4 or greater on the scale were coded as having the frailty characteristic of fatigue. 188 of the 1027 were coded as missing.

Physical activity levels—Self-reported physical activity levels ranged from 0-6, with high scores denoting greater physical activity.[26] If participants scored 1 or 2, they were coded as having the frailty characteristic of low physical activity levels. 75 of the 1027 were coded as missing.

DEPRESSION

Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D[27]). The scale ranges from 0 to 60 with high scores indicative of greater depressive symptomatology. Scores were presented categorically as *nondepressed* (CES-D ≤ 9), *mildly depressed* (CES-D between 10-15), and *depressed* (CES-D ≥ 16). A cut-off score of ≥ 16 correlates with the presence of a depressive disorder.[28, 29]

MORTALITY

Time of death for all participants who died following initial assessment was obtained from the official register or from hospital records. Death records were last updated in the fall of 2000, providing a maximum follow-up from initial evaluation of 11.08 years (survival: mean [SD], 10.48 years [.59]; mortality: mean [SD], 5.44 years [2.83]).

Secondary variables (instrumental activities of daily living [IADLs], number of chronic illnesses, and neuropsychological measures of processing speed[30, 31] and executive function[10, 12] [Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale-Revised[32] and Raven's Progressive Matrices[33]]) are included in preliminary analyses.

Statistical Analysis

Analysis of variance or χ^2 tests were used to detect differences across the three depressed groups and between men and women for baseline continuous and categorical variables. Post hoc analyses compared only nondepressed and depressed groups. Nonparametric Kruskal-Wallis or Mann-Whitney U procedures were used for variables with skewed distributions across groups. Survival time from baseline was the main outcome, with time observed either to death or to last follow up. We estimated survival curves using the Kaplan-Meier method to examine the pattern in survival time and used log rank tests to detect group differences in the survival curves. An initial omnibus site-stratified Cox proportional hazard model was conducted examining the relationship between gender, total frailty characteristics, and depressive symptoms in the total sample, χ^2_5= 80.52, P < .001. This model identified a main effect of total frailty characteristics, Wald χ^2_1= 7.76, P = .005 *(*HR, 1.62; 95% CI, 1.15-2.26) and a gender × depressive symptoms interaction, Wald χ^2_1= 5.95, P = .015 *(*HR, 1.04; 95% CI, 1.01-1.07). Given the significant gender × depression interaction, gender-stratified Cox proportional hazard models were used to examine the effects of frailty characteristics, depression, and depression by frailty characteristic interactions on survival time. Dummy coded variables for frailty, missing data, and depression status were used for single predictor models. For these single predictor models, Bonferroni correction on the false-positive error rate was used to account for multiple comparisons (α of .05 adjusted for four frailty characteristics: α = .0125). Multiple predictor models were used to explore the simultaneous effects of the baseline frailty characteristics in nondepressed and depressed men and women. Hazard ratios with 95% confidence interval were derived to aid interpretation. Age was not entered into the models because participants were all 75 years of age at baseline. Education was not entered because it was coded differently across the three research sites and missing in most participants. Models were conducted with and without number of chronic baseline illnesses entered as a covariate.

Results

Frailty and Depression at Baseline—Baseline demographics, frailty characteristics (total number and values on each individual characteristic), IADLs, number of chronic illnesses, and neuropsychological variables differed by depressed group (Table 1). Total number of frailty characteristics increased across groups (H_2 = 28.74, P < .001) with the depressed group having more frailty characteristics than the nondepressed group. Individual

frailty characteristics gait speed ($F_{2, 879}$ = 14.13, P < .001), physical activity level ($F_{2, 949}$ = 14.73, P < .001), grip strength ($F_{2, 851}$ = 21.90, P < .001), and levels of fatigue ($H_{2,}$= 54.05, P < .001) differed by depression status, with each more impaired in the depressed than the nondepressed group. Additionally, IADLs (H_2 = 71.28, P < .001), number of chronic illnesses (H_2 = 27.85, P < .001), Digit Symbol Substitution Test ($F_{2, 907}$ = 26.91, P < .001) and Raven's Progressive Matrices ($F_{2, 909}$ = 20.99, P < .001) differed by depression status, with the depressed group showing greater impairment than the nondepressed group. Mortality rates were related to depression status in the sample of 1027 elderly, χ^2_2 = 6.93, P = .03, with the rate in the depressed group (54%) greater than that of the nondepressed group (45%).

Baseline differences were also observed between men and women (Table 2). Women presented with greater depressive symptoms, more impairment in IADLs, and worse performance on Raven's Progressive Matrices compared with men. There were no gender differences on number of chronic illnesses or Digit Symbol Substitution Test. More women had gait impairment, greater fatigue, and lower physical activity levels compared with men; no gender differences were observed, however, for impaired grip strength (Table 2). Mortality rates were related to gender, χ^2_2 = 20.68, P < .001; more men died (55%) than did women (41%).

To investigate the relationship between depression and individual frailty characteristics on mortality, a series of site-stratified gender specific Cox regression models were conducted.

Gait Speed—Cox regression models with depression, gait speed, and missing gait speed data predicted survival in men (n = 362; χ^2_5 = 46.98, P < .001) and women (n = 442; χ^2_3 = 42.19, P < .001). In men, there was a main effect of gait impairment (Wald χ^2_1= 11.32, P = .001; HR, 1.85; 95% CI, 1.29-2.64) and a depression by missing gait data interaction (Wald χ^2_1= 7.29, P = .007; HR, 3.39; 95% CI, 1.40-8.21). In women, there was a main effect of depression (Wald χ^2_1= 6.33, P = .012; HR, 1.47; 95% CI, 1.09-1.98), gait impairment (Wald χ^2_1= 15.51, P < .001; HR, 1.99; 95% CI, 1.41-2.81), and missing gait data (Wald χ^2_1= 28.84, P < .001; HR, 3.07; 95% CI, 2.04-4.63); no interactions were observed. The inclusion of number of chronic health illnesses as a covariate did not impact the model in men; in women, its inclusion diminished the effect of depression status on survival.

Grip Strength—Cox regression models with depression, grip strength, and missing grip strength data predicted survival in men (n = 362; χ^2_5 = 22.59, P < .001) and women (n = 442; χ^2_3 = 30.43, P < .001). In men, there was a depression by missing grip strength data interaction (Wald χ^2_1= 8.57, P = .003; HR, 3.66; 95% CI, 1.54-8.71). In women, there was a main effect of grip impairment (Wald χ^2_1= 6.30, P = .012; HR, 1.59; 95% CI, 1.11-2.82), and missing grip strength data (Wald χ^2_1= 18.70, P < .001; HR, 2.24; 95% CI, 1.55-3.22); no interactions were observed. The inclusion of the covariate did not impact the model in men or women.

Fatigue—Cox regression models with depression, fatigue, and missing fatigue data predicted survival in men (n = 362; χ^2 = 39.88, P < .001) and women (n = 442; $\chi^2_{5\,3}$ = 31.69, P < .001). In men, there was a main effect of fatigue (Wald χ^2_1= 8.03, P = .005; HR,

1.75; 95% CI, 1.19-2.57) and missing fatigue data (Wald χ^2_1= 7.86, P = .005; HR, 2.95; 95% CI, 1.22-3.10). In women, there was a main effect of fatigue (Wald χ^2_1= 11.61, P = .001; HR, 1.87; 95% CI, 1.30-2.67) and missing fatigue data (Wald χ^2_1= 17.86, P < .001; HR, 2.21; 95% CI, 1.53-3.19). No interactions were observed. The inclusion of the covariate did not impact the model in men or women.

Physical Activity Levels—Cox regression models with depression, physical activity, and missing physical activity data predicted survival in men (n = 362; χ^2_3 = 37.38, P < .001) and women (n = 442; χ^2_3 = 33.50, P < .001). In men, there was a main effect of low physical activity (Wald χ^2_1= 27.69, P < .001; HR, 2.37; 95% CI, 1.72-3.26) and missing physical activity data (Wald χ^2_1= 12.54, P < .001; HR, 2.64; 95% CI, 1.54-5.53). In women, there was a main effect of low physical activity (Wald χ^2_1= 19.82, P < .001; HR, 2.11; 95% CI, 1.52-2.93), and missing physical activity data (Wald χ^2_1= 8.05, P = .005; HR, 1.97; 95% CI, 1.23-3.15). The inclusion of the covariate did not impact either model.

Gender, Frailty, and Depression—The survival curves displayed in Figure 1 illustrate that frailty characteristics, missing data on these frailty characteristics, and depression affect survival in both men and women. To explore the most salient frailty characteristics in predicting mortality in both nondepressed and depressed men and women, four multiple-predictor, site-stratified models were conducted. Each model [nondepressed men (n = 278; χ^2_8 = 33.95, P < .001), nondepressed women (n = 265; χ^2_8 = 25.20, P = .001), depressed men (n = 84; χ^2_8 = 31.51, P < .001), and depressed women (n = 177; χ^2_8 = 32.00, P < .001)] predicted risk of death.

The pattern differed by gender and depression status (Table 3). For nondepressed men low physical activity, missing physical activity data, and impaired gait speed increased risk of death after controlling for the effect of all other frailty characteristics. In nondepressed women only impaired grip strength was predictive of death. In depressed men only missing fatigue data increased risk of death. In depressed women, however, impaired gait speed and fatigue were associated with higher risk of death, although the overall effect of fatigue was not significant due to the lack of effect of missing data on the fatigue assessment. Inclusion of number of chronic health illnesses as a covariate did not contribute to either depressed model. In nondepressed men, its inclusion decreased the effect of fatigue and gait impairment on survival. In the nondepressed women, its inclusion decreased the effect of low physical activity and fatigue, and increased the effect of gait and grip impairment on survival.

As depicted in Figure 1A, depression did little to alter the effect of impaired gait speed on mortality in men (mortality rates, nondepressed men: no gait impairment = 48%; gait impairment = 75%; depressed men: no gait impairment=45%; gait impairment = 71%). In women, however, the effect of impaired gait speed on mortality nearly doubled when depression was present (mortality rates, nondepressed women: no gait impairment = 26%; gait impairment = 40%; depressed women: no gait impairment=32%; gait impairment = 58%). A similar pattern was observed for fatigue (Figure 1C).

Conclusions

The syndrome of frailty and depressive illness are each associated with increased disability and death, but the confluence of each has rarely been studied.[1, 2, 4, 16, 19, 20, 31, 34-41] This study investigated the relationship between depressive symptoms, characteristics of frailty, and mortality in 75-year old men and women. The results show that 1) the effect of each frailty characteristic, missing data on each frailty characteristic, and depression status on progression to death differed between men and women; 2) in depressed men, missing data on the assessment of gait speed, grip strength, or fatigue resulted in an increased risk of death; and 3) the combined effect of depression and characteristics of frailty, specifically fatigue and impaired gait speed, on mortality is particularly deleterious for older women.

The study hypothesis that impaired gait speed and grip strength would be the most salient characteristics for predicting mortality in the older depressed group was only partially observed. Low grip strength was only predictive of mortality in women, independent of depression status, and only when none of the other frailty characteristics were considered. Subgroup analysis showed that mobility disturbance and fatigue were strongly associated with increased risk of death in older depressed women. These results are consistent with past research demonstrating the impact fatigue and worsening mobility have on prognosis,[24, 42-46] although these studies did not account for depression. Frailty characteristics have been shown to induce a self-perpetuating cycle that develop incrementally with weakness emerging early in the process and weight loss and fatigue representing a final pathway towards frailty.[1-3] Fatigue, however, is a common symptom in late life depression and can effect prognosis in elderly people.[47] These findings, particularly those observed in depressed women, emphasize the importance of accounting for the presence of depression in frailty research; depressed elders may have a different level of impairment and a different clinical course.

The presence of depressive illness in the context of frailty has until recently[21] been largely ignored.[16, 19, 20] The adverse effect of depression on frailty characteristics in this study however was pervasive, with depressive symptoms associated with increased weakness, mobility deficits, and fatigue, as well as illness burden, and neuropsychological impairment.[11, 12, 21, 48-51] Although these findings highlight the strength and severity of these associations, currently the nature of the relationship between the syndrome of frailty and depressive illness remains unclear. There are a number of possible models to explain the depressed-frail phenotype. First, the two conditions may be unrelated to each other but frequently coexist in the elderly (as with cataracts and arthritis). Second, one condition may be a risk factor for developing the other. In this model it is critical to know whether their onset is concurrent or whether one generally precedes the other. Third, the relationship maybe an illusion; two disorders that appear to be distinct are really different manifestations of the same disorder. For example, there is now evidence to suggest that depression is an early symptom of Huntington's disease rather than a separable diagnosis.[52] Longitudinal data need to be examined to test these models.

Research examining the nature of the relationship between depressive illness and the syndrome of frailty in late life will have treatment implications. Currently, there are multiple nonpharmacological treatments such as exercise or nutritional interventions[53-57] that have

been designed to improve strength in lower extremities to improve mobility and decrease fall potential.[4] Questions remain however about the utility of these interventions in depressed elders, as these studies typically exclude patients with depressive illness and the overall effectiveness of exercise interventions as a treatment for depression is at best mixed.[58-60] Likewise, although antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective for the treatment of late life depression,[61] there is currently no evidence that these medications can effectively treat characteristics of frailty, particularly characteristics such as slowed gait speed that are strongly associated with mortality. Given these findings, an important direction for future research would be an investigation of the effectiveness of antidepressant medication on frailty characteristics in older depressed frail patients, as well as the feasibility and effectiveness of multimodal interventions (exercise and antidepressant medication) to improve prognosis in older depressed prefrail and frail individuals. Although side effect profiles in older depressed patients appear similar to those of younger depressed patients,[62] caution must be taken with SSRI use in a prefrail or frail geriatric population as treatment with these medications is associated with increased risk of falls,[63] hyponatremia, and bleeding.

There are important limitations to this study. The NORA study included 75-year old men and women from Glostrup in Denmark, Göteborg in Sweden and Jyväskylä in Finland; the generalizability of these results to other localities may be limited. Also, the use of the CES-D as a diagnostic tool for depressive illness is suboptimal. The cut-off of ≥ 16 used to denote depression, however, has been shown to have 100% sensitivity and 88% specificity for major depressive disorder in elders.[27-29] Of note, individuals with missing data on frailty characteristics do not appear to represent a random sample; we can only hypothesize the meaning behind the missing data and its relationship to outcome, which is included in supplemental material online. Additionally, this investigation has limited power to assess interactions between depression and each of the frailty characteristics in the multiple predictor models due to sample size constraints. As such, subgroup analyses were used and interpretation of these results should be made with caution. Future research is needed to better understand the interrelationships between depression and individual frailty characteristics and their impact on prognosis.

In conclusion, this study showed that the confluence of characteristics of frailty (fatigue, slow gait speed) and depressive illness resulted in an increased risk of death in older adults; specifically, the presence of depression nearly doubled the effect of fatigue and slow gait speed on mortality rates in older women. Future research should investigate whether multimodal interventions targeting depressive illness, mobility deficits, and fatigue can decrease mortality and improve quality of life in older depressed individuals with characteristics of the syndrome of frailty.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Brown had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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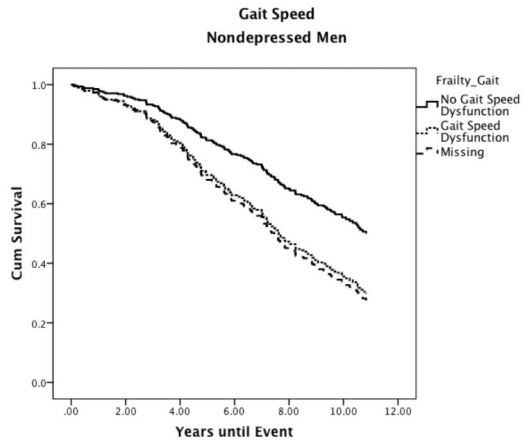

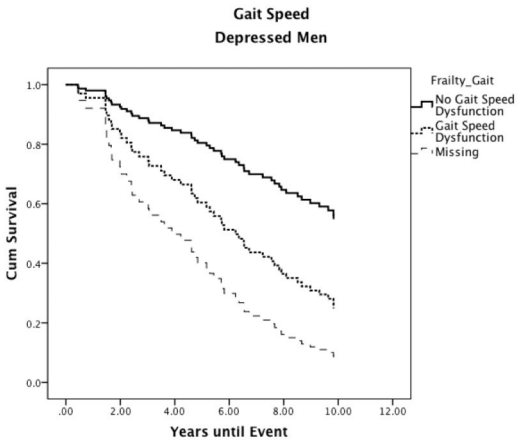

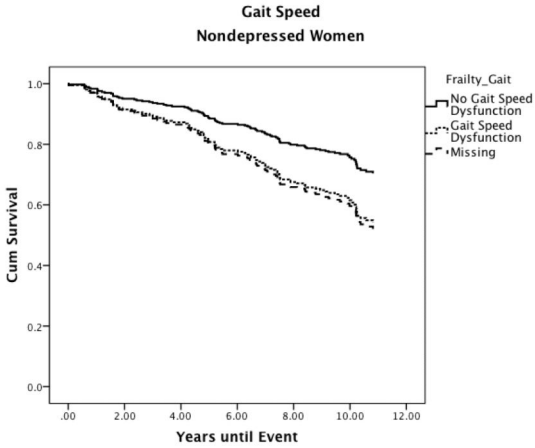

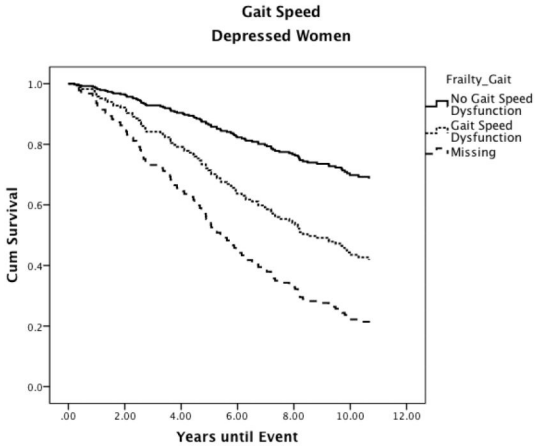

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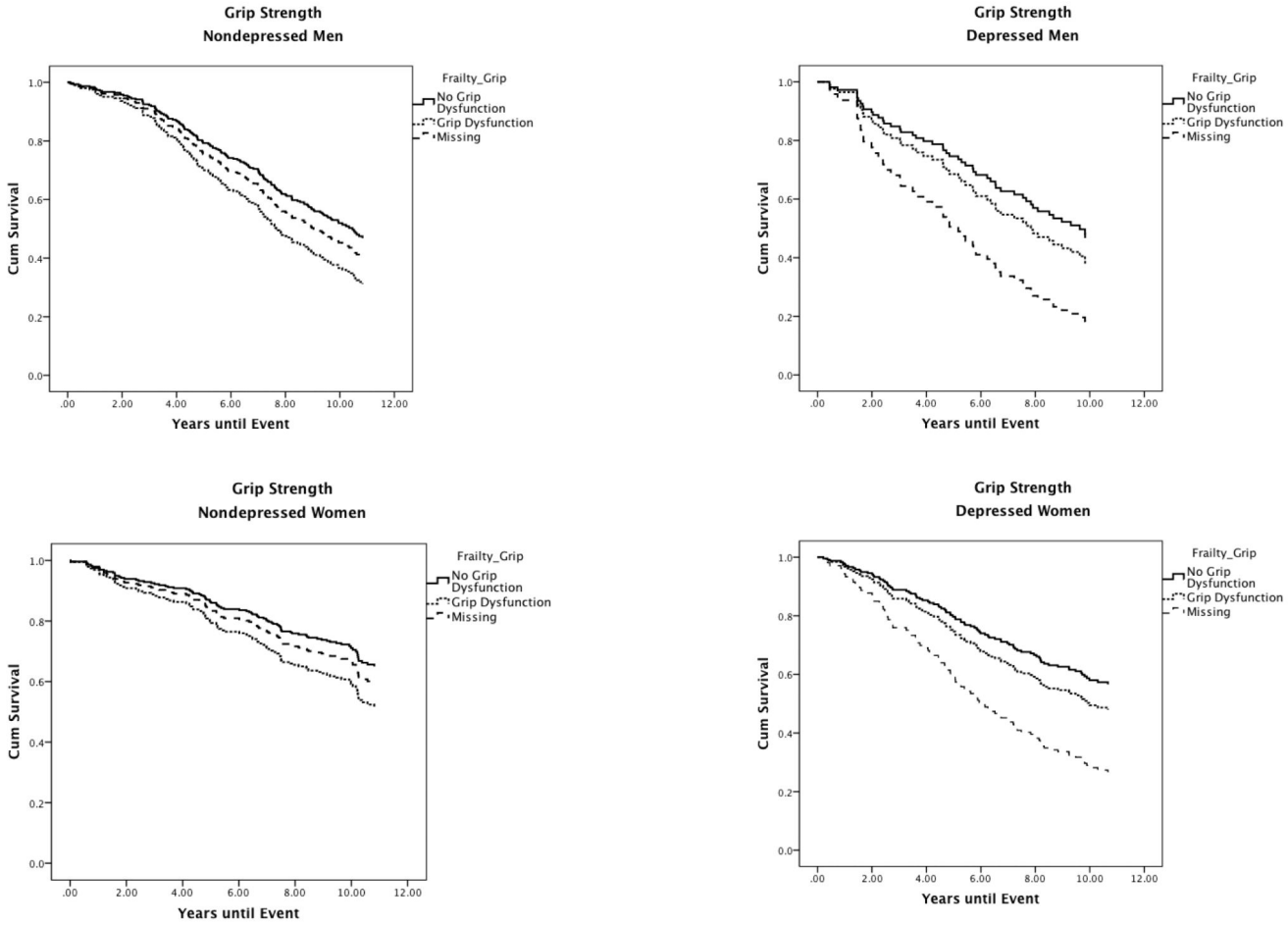

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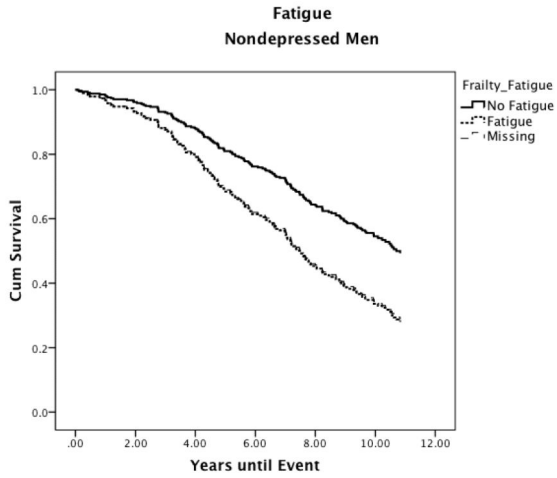

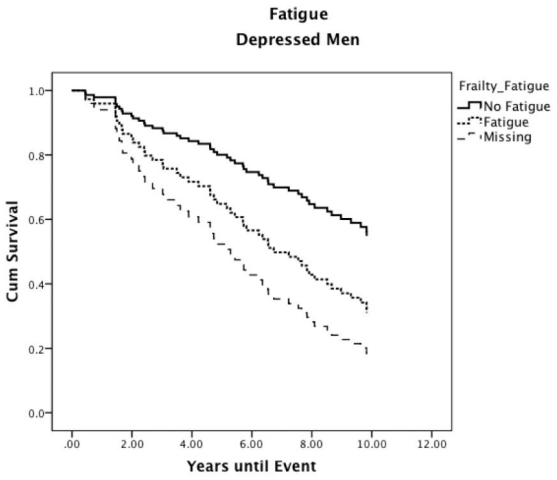

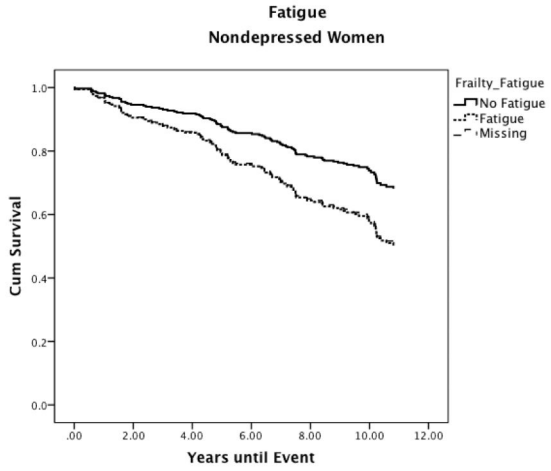

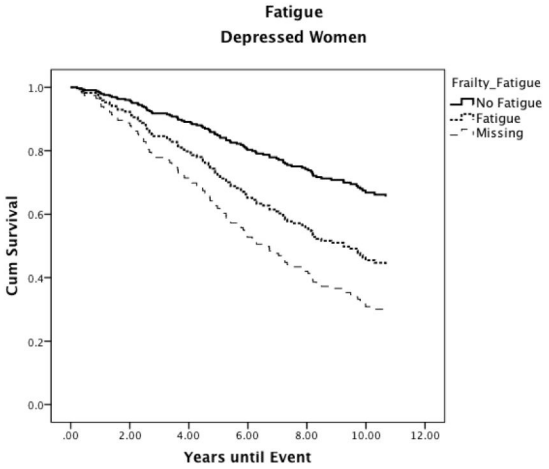

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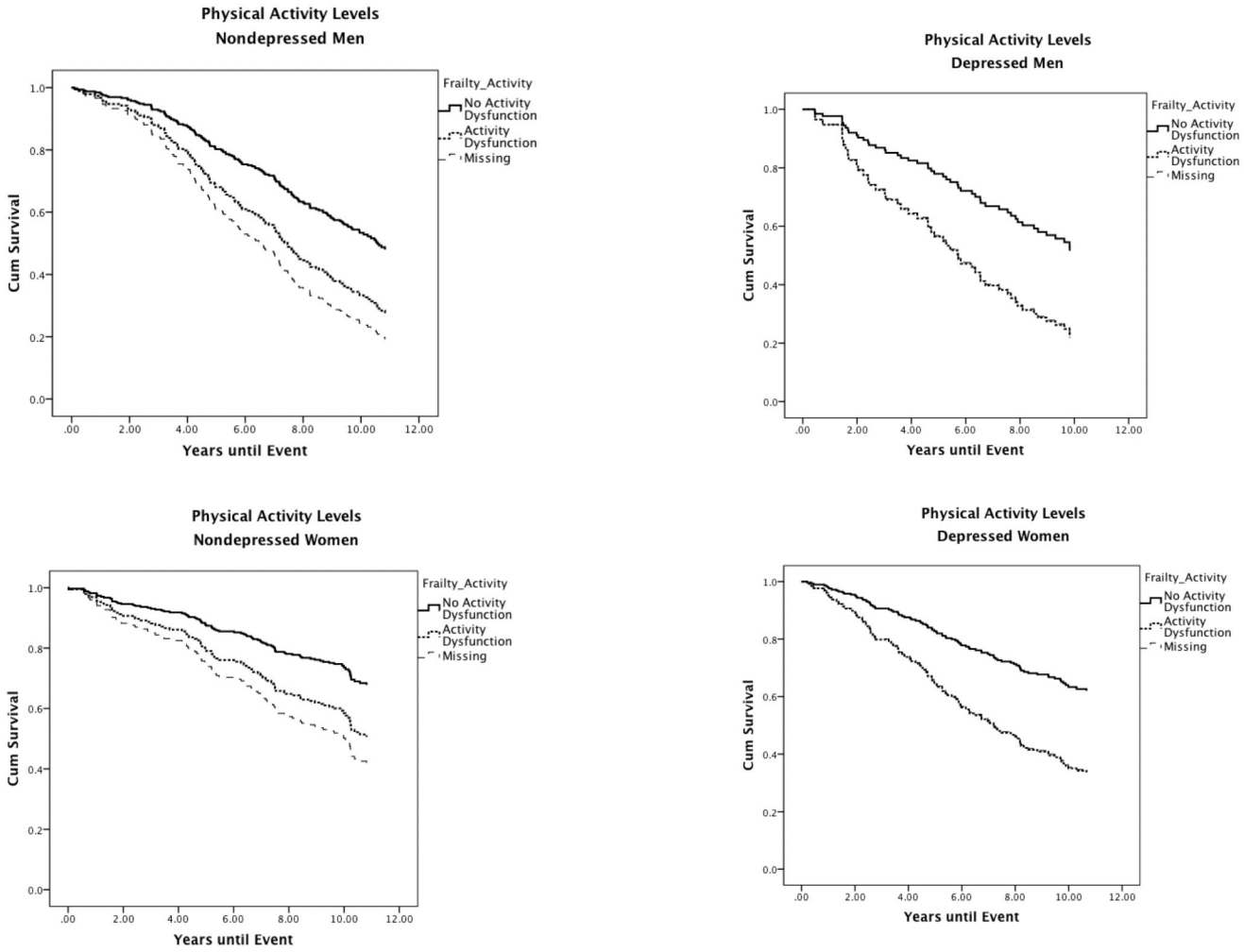

Figure 1.

Site stratified single predictor Kaplan-Meier survival curves for individual frailty characteristics in depressed and nondepressed men and women.

Note. Nondepressed = Center for Epidemiologic Studies Depression Scale less than or equal to 9; Depressed = Center for Epidemiologic Studies Depression Scale greater than or equal to 16; Gait Speed: No Gait Speed = Walking speed in meters per second in the gender-specific top 75th percentile; Gait Speed Dysfunction = Walking speed in meters per second in the gender-specific bottom 25th percentile (men: less than or equal to 1.43 m/s; women: less than or equal to 1.25 m/s); Grip Strength: No Grip Dysfunction = Grip strength in kilograms of force in the gender-specific top 75th percentile; Grip Dysfunction = Grip strength in kilograms of force in the gender-specific bottom 25th percentile (men: less than or equal to 36.71 kg; Women: less than or equal to 20.90 kg); Fatigue: No Fatigue = Individuals who scored less than 4 on the fatigue scale (denoting less exhaustion on select activities) scored in the top 75th percentile. Fatigue: Individuals who scored 4 or greater on the Fatigue scale (denoting greater Fatigue) scored in the bottom 25th percentile; Physical Activity Levels: No Physical Activity Dysfunction = Individuals who responded to the

statement: Free time activity over the past year is best described as: moderate physical activity about 3 hours per week (3), moderate physical activity over 4 hours per week or intense physical activity up to 4 hours per week (4), active sports at least 3 hours per week (4), competitive sports (6) were in the top 75th percentile. Physical Activity Dysfunction = Individuals who responded to the statement Free time activity over the past year is best described as: mainly sitting in one place (1) or light physical activity (2) were in the bottom 25th percentile.

Table 1

Baseline characteristics for nondepressed, mildly depressed, and depressed groups[a]

Variables	Nondepressed (n = 543)	Mildly Depressed (n = 223)	Depressed (n = 261)
	Mean (SD)	Mean (SD)	Mean (SD)
Sex, No. M/F (% F)	278/265 (49%)	74/149 (67%)	84/177 (68%) [b]
Mortality, No. Alive/Dead (% Dead)	299/244 (45%)	125/98 (44%)	120/141 (54%) [b]
CES-D	4.14 (3.07)	12.47 (1.68)	23.26 (7.26) [b]
Number of Chronic Illnesses [τ]	n = 280	n = 141	n = 156
	1.95 (1.44)	2.31 (1.42)	2.69 (1.49) [b]
Neuropsychological scores			
Digit Symbol	n = 493	n = 193	n = 224
	30.30 (12.26)	25.81 (10.11)	24.09 (10.21) [b]
Raven's Matrices (number correct)	n = 489	n = 195	n = 228
	17.23 (4.45)	15.99 (4.23)	14.96 (4.73) [b]
Functioning			
IADLs [τ]	1.44 (2.16)	2.01 (2.48)	3.31 (3.44) [b]
Frailty Characteristics			
Total Frailty Characteristics [τ]	n = 389	n = 149	n = 155
Mean	.91 (0.99)	.91 (1.01)	1.43 (1.11) [b]
No. ≥ 3 frailty characteristics (% Frail)	27 (7%)	15 (10%)	33 (21%)
Gait Speed (m/s)	n = 479	n = 186	n = 217
Mean	1.63 (0.41)	1.56 (0.38)	1.45 (0.41) [b]
Frailty, No. Yes/No (% Frail)	163/316 (34%)	64/122 (34%)	107/110 (49%) [b]
Grip Strength (kg/f)	n = 460	n = 187	n = 207
Mean	35.28 (12.57)	29.69 (10.20)	30.07 (11.75) [b]
Frailty, No. Yes/No (% Frail)	95/365 (21%)	57/130 (31%)	70/137 (34%) [b]
Fatigue Levels [τ]	n = 470	n = 179	n = 190
Mean	1.57 (2.09)	1.75 (1.99)	2.84 (2.22) [b]
Frailty, No. Yes/No (% Frail)	104/366 (22%)	35/144 (20%)	82/108 (43%) [b]
Physical Activity Levels	n = 509	n = 207	n = 236
Mean	3.10 (0.91)	2.92 (0.93)	2.70 (1.01) [b]
Frailty, No. Yes/No (% Frail)	118/391 (23%)	64/143 (31%)	101/135 (43%) [b]

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale; *Nondepressed* = CES-D less than or equal to 10; *Mildly depressed* = CES-D greater than or equal to 10 but less than 16; and *Depressed* = CES-D greater than or equal to 16; Digit Symbol = Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale-Revised; Raven's Matrices = Raven's Progressive Matrices; IADLs = Instrumental Activities of Daily Living.

[a] Data are presented as means (SD) unless otherwise indicated. Neuropsychological scores are raw scores. Analysis of variance F-tests or χ^2 tests were used to detect overall group differences across the three depressed groups for continuous and categorical variables, but only two post hoc group comparisons (nondepressed vs. depressed) were made. Sample sizes are indicated for variables with missing data.

[τ] Nonparametric Kruskal-Wallis tests were used to detect overall and pairwise group differences for variables with skewed distributions.

[b] Significant difference in post hoc parametric or nonparametric comparisons between nondepressed and depressed individuals ($P \leq .05$).

Table 2

Baseline characteristics for men and women in the Nordic Research on Ageing Project[a]

Variable	Women (n = 591)	Men (n = 436)
	Mean (SD)	Mean (SD)
CES-D	12.29 (9.51)	8.81 (8.06) [b]
Number of Chronic Illnesses	n = 350	n = 227
	2.24 (1.50)	2.22 (1.44)
Neuropsychological scores		
Digit Symbol	n = 515	n = 395
	28.65 (11.77)	28.05 (11.54)
Raven's Matrices (number correct)	n = 519	n = 393
	15.79 (4.30)	17.21 (4.79) [b]
Functioning		
IADLs [τ]	2.33 (2.73)	1.66 (2.67) [b]
Frailty Characteristics		
Total Frailty Characteristics [τ]	n = 382	n = 311
Mean	1.12 (1.05)	.91 (1.01) [b]
No. ≥ 3 frailty characteristics (% Frail)	52 (14%)	23 (7%)
Gait Speed (m/s)	n = 479	n = 377
Mean	1.47 (0.35)	1.71 (0.44) [b]
Frailty, No. Yes/No (% Frail)	235/270 (49%)	99/278 (26%)
Grip Strength (kg/f)	n = 482	n = 372
Mean	25.03 (6.82)	42.86 (10.04) [b]
Frailty, No. Yes/No (% Frail)	124/358 (26%)	98/274 (26%)
Fatigue Levels [τ]	n = 463	n = 376
Mean	2.00 (2.14)	1.77 (2.18) [b]
Frailty, No. Yes/No (% Frail)	128/335 (28%)	93/283 (25%)
Physical Activity Levels	n = 542	n = 410
Mean	2.89 (0.88)	3.06 (1.04) [b]
Frailty, No. Yes/No (% Frail)	176/366 (33%)	107/303 (26%)

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale; Digit Symbol = Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale-Revised; Raven's Matrices = Raven's Progressive Matrices; IADLs = Instrumental Activities of Daily Living.

[a] Data are presented as means (SD) unless otherwise indicated. Neuropsychological scores are raw scores. Sample sizes are indicated for variables with missing data. Independent sample t-tests or χ^2 tests were used to detect gender differences for continuous or categorical variables.

[τ] Nonparametric Mann-Whitney U tests were used to detect gender differences for variables with skewed distributions.

[b] Significant difference between men and women ($P \leq .05$).

Table 3

Site stratified proportional hazards models with multiple predictors of frailty characteristics for depressed and nondepressed men and women.

	Nondepressed (n=543)						Depressed (n=261)					
	Men (n=278)			Women (n=265)			Men (n=84)			Women (n=177)		
Frailty Predictors	**Wald χ^2**	**Hazard ratio (95% CI)**	**p Value**	**Wald χ^2**	**Hazard ratio (95% CI)**	**p Value**	**Wald χ^2**	**Hazard ratio (95% CI)**	**p Value**	**Wald χ^2**	**Hazard ratio (95% CI)**	**p Value**
Low Physical Activities	10.48		0.005	1.25		0.535	1.81		0.404	3.66		0.160
Yes vs. No	7.27	1.76 (1.17, 2.65)	0.007	1.13	1.34 (0.78, 2.28)	0.287	1.61	1.68 (0.76, 3.74)	0.204	2.86	1.56 (0.93, 2.61)	0.091
Missing vs. No	4.85	2.80 (1.12, 7.01)	0.028	0.01	0.95 (0.36, 2.50)	0.917	0.09	1.25 (0.29, 5.46)	0.765	0.19	0.81 (0.32, 2.05)	0.662
Fatigue	4.90		0.086	3.67		0.160	6.46		0.040	5.62		0.060
Yes vs. No	3.82	1.51 (1.00, 2.28)	0.051	2.73	1.54 (0.92, 2.56)	0.098	1.02	1.48 (0.69, 3.15)	0.313	5.40	1.94 (1.11, 3.40)	0.020
Missing vs. No	2.24	1.46 (0.89, 2.41)	0.134	1.96	1.52 (0.85, 2.74)	0.161	6.29	2.90 (1.26, 6.67)	0.012	2.81	1.66 (0.92, 3.00)	0.094
Slow Gait Speed	5.99		0.050	1.89		0.388	2.17		0.338	6.69		0.035
Yes vs. No	4.96	1.54 (1.05, 2.26)	0.026	1.04	1.30 (0.79, 2.14)	0.307	1.01	1.52 (0.67, 3.45)	0.315	4.59	1.84 (1.05, 3.21)	0.032
Missing vs. No	1.92	1.71 (0.80, 3.64)	0.166	1.38	1.85 (0.66, 5.18)	0.240	1.95	2.67 (0.67, 10.59)	0.163	5.47	2.71 (1.18, 6.26)	0.019
Low Grip Strength	2.34		0.310	4.92		0.085	0.64		0.725	1.60		0.452
Yes vs. No	0.01	1.02 (0.65, 1.59)	0.934	4.64	1.83 (1.06, 3.18)	0.031	0.63	1.35 (0.64, 2.81)	0.429	0.43	1.19 (0.70, 2.02)	0.513
Missing vs. No	2.19	0.55 (0.25, 1.22)	0.139	0.85	1.52 (0.63, 3.69)	0.355	0.05	1.15 (0.33, 4.02)	0.827	1.46	1.59 (0.75, 3.36)	0.228

Cox proportional hazard models were used to explore the simultaneous effects of the baseline frailty characteristics in separate models for nondepressed and depressed men and women. Wald χ^2 values are listed; (df = 2 for the overall effect of each frailty characteristic, df= 1 for each subgroup comparison); Hazard ratios (and 95% CI) are for multiple predictor models with the inclusion of other frailty characteristics as covariates.