Physical frailty in late-life depression: evidence for a depression-frailty subtype?

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Chapter II

The relation between physical frailty and low-grade inflammation in late-life depression

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Abstract

Objectives - To determine whether physical frailty is associated with low-grade inflammation in older adults with depression, because late-life depression is associated with frailty and low-grade inflammation.

Design - Baseline data of a cohort study.

Setting- Primary care and specialized mental health care.

Participants - Individuals aged 60 and older with depression according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria (N=366).

Measurements - The physical frailty phenotype, defined as three out of five criteria (weight loss, weakness, exhaustion, slowness, and low physical activity level), and three inflammatory markers (C-reactive protein (CRP), interleukin-6 (IL-6) and neutrophil gelatinase-associated lipocalin (NGAL) were assessed.

Results - The physical frailty phenotype was not associated with inflammatory markers in linear regression models adjusted for sociodemographic characteristics, lifestyle characteristics and somatic morbidity. Of the individual criteria, handgrip strength was associated with CRP (β=-0.21, p=.002) and with IL-6 (β=-0.25, p<.001), and gait speed was associated with NGAL (β=0.15, p=.02). Principal component analysis identified two dimensions within the physical frailty phenotype: performance-based physical frailty (encompassing gait speed, handgrip strength and low physical activity) and vitality-based physical frailty (encompassing weight loss and exhaustion). Only performance-based physical frailty was associated with higher levels of inflammatory markers (CRP: β=0.14, p=.031; IL-6: β=0.13, p=.060; NGAL: β=0.14, p=.028).

Conclusion- The physical frailty phenotype is not a unidimensional construct in individuals with depression. Only performance-based physical frailty is associated with low-grade inflammation in late-life depression, which might point to a specific depressive subtype.

Introduction

Frailty is a medical syndrome describing persons at greater risk of adverse health outcomes when exposed to a stressor (Morley et al., 2013). Frailty is considered an important syndrome for geriatric health care, because frail persons are high users of community resources, hospitalization, and nursing homes. Therefore, early intervention may improve quality of life and reduce costs of care (Morley et al., 2013). The mean prevalence rate of physical frailty is estimated 9.9% in community-dwelling persons aged 65 and older (range 4.0 – 17.0%) (Collard et al., 2012).

Although the criteria for physical frailty and depression partly overlap, both represent unique, but reciprocally related constructs (Mezuk et al., 2012). Two models of physical frailty are dominant (Fried et al., 2001; Rockwood & Mitnitski, 2011). The deficit model of Rockwood consists of adding together an individual's number of impairments and conditions to create a Frailty Index (Rockwood & Mitnitski, 2011). The physical frailty phenotype of Fried, as included in the current study, consists of a constellation of three out of five possible criteria (weight loss, exhaustion, weakness, slowness, and reduced physical activity) (Fried et al., 2001). It was recently shown that 27% of older persons with depression met the criteria for the physical frailty phenotype (Collard et al., 2014). The physical frailty phenotype is assumed to mark an underlying physiological state of multisystem and energy dysregulation (Fried et al., 2004). Depressive disorder is increasingly recognized as a disorder of accelerated aging (Verhoeven et al., 2014), sharing at least some underlying pathophysiological mechanisms with physical frailty (Révész et al., 2014). It has been proposed that immunosenescence is one of the mechanisms underlying frailty. Ageing of the immune system results in a condition of chronic low-level inflammation, also called "inflamm-ageing" (De Martinis et al., 2006), characterized by high levels of the inflammatory cytokine interleukin-6 (IL-6) and the non-specific acute phase reactant C-reactive protein (CRP) (Moshage, 1997). Frailty and depression have been associated with higher serum CRP and IL-6 levels (Bremmer

et al., 2008). High circulating levels of neutrophil gelatinase-associated lipocalin (NGAL), an acute phase protein, have recently been found in aging-related disorders such as mild cognitive impairment, Alzheimer's disease and late-life depression (Choi et al., 2011; Naudé et al., 2013). The association between inflammation and frailty has been reported consistently, in contrast to the association between inflammation and late-life depression (Bremmer et al., 2008; Milaneschi et al., 2009). Low-grade inflammation in late-life depression might thus depend on the level of frailty.

The present study examined whether the physical frailty phenotype is associated with low-grade inflammation in older adults with depression. It was hypothesized that inflammatory markers would be found to be associated with the physical frailty phenotype and that the frailty criteria that do not overlap with the depression criteria (muscle strength and gait speed) would be found to determine this association.

Methods

Study population - The present study was embedded within the Netherlands Study of Depression in Older persons (NESDO) (Comijs et al., 2011). The NESDO sample consists of 378 subjects aged 60 years and older with a current diagnosis of 6-month major depressive disorder (95%), minor depression (5.6%) or dysthymia (26.5%). Diagnoses were established according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) using the Composite International Diagnostic Interview version 2.1 (Wittchen et al., 1991). Three hundred twenty-six of the participants (86.2%) were recruited from mental health institutes (in- and outpatients) and 52 (13.8%) from primary care.

Exclusion criteria were a diagnosis of dementia, a Mini-Mental State Examination (MMSE) score less than 18, an organic or psychotic disorder, and finally insufficient mastery of the Dutch language (Comijs et al., 2011).

All participants underwent a baseline examination at one of the five research locations (University Medical Center Groningen, Free University Medical Center Amsterdam, Leiden University Medical Center, Radboud University Medical Center, Mental Health Care Center GGNet) or at the home. The ethical review boards of all participating study centers approved of the study protocol, and all participants provided written informed consent (Comijs et al., 2011).

Physical frailty phenotype - The physical frailty phenotype was assessed according to the Fried criteria (Fried et al., 2001). A person is classified as frail when at least three out of the following five criteria are present (Collard et al., 2014):

- *Unintentional weight loss:* unwanted weight loss of 1 kg/wk or more during two or more consecutive weeks or a body mass index (BMI) of less than 18.5 kg/m².
- *Weakness:* based on the maximum handgrip strength of the dominant hand assessed using a handgrip dynamometer. The best out of two trials was stratified according to sex and BMI quartile (Fried et al., 2001).
  Participants unable to perform the test were also considered weak.
- *Exhaustion:* determined according to two questions from the Center for Epidemiologic Studies Depression scale (Radloff, 1977), as in previous studies (Fried et al., 2001): "I felt that everything I did was an effort" and "I could not get going." Participants answering "3 or more days a week" to either of these two items were categorized as positive.
- *Slowness:* measured using the 6-m walking test, using sex- and body height-stratified cutoffs as extrapolated from Fried et al. 5 (9 seconds for men ≤173 cm and women ≤159 cm tall; 8 seconds for men >173 cm and women >159 cm) (Fried et al., 2001).
- *Low physical activity level:* no daily activities such as walking and gardening and sports activity less than once weekly, as assessed according to short form of the International physical Activities Questionnaire (IPAQ) (Kriegsman et al., 1996).

Inflammatory markers - Fasting blood samples were obtained and kept at −80°C for subsequent analyses. Plasma CRP, IL-6 and NGAL levels were assessed. Plasma levels of high-sensitivity CRP were measured in duplicate using a immunoturbidimetric assay (Tina-quant CRPHS; Roche Diagnostics, Mannheim, Germany). Intra- and interassay coefficients of variation were both 2%. Plasma IL-6 levels were measured in duplicate using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit (PeliKine Compact ELISA; Sanquin, Amsterdam, the Netherlands). Intra- and interassay coefficients of variation were 8% and 12%, respectively.
Finally, the plasma NGAL levels (ng/ml) were measured in duplicate using an ELISA kit (R&D Systems, Minneapolis, MN) (Naudé et al., 2013). The intra- and interassay coefficients of variation were 2% and 5%, respectively.

Covariates - Demographic data were collected on age, sex, and years of education, as well as lifestyle and disease-related characteristics that are potentially associated either inflammatory markers or physical frailty.
Lifestyle characteristics included smoking (yes/no), alcohol intake (no drinking/moderate drinking/problematic drinking (5 – 10 units on a typical drinking day regardless of the frequency of drinking or 3 or 4 units on a typical drinking day at least 4 days a week)), physical activity (measured using the IPAQ in metabolic equivalent minutes (ratio of energy expenditure during activity to rest times the number of minutes performing the activity per week)), and BMI.
Disease-related covariates included global cognitive functioning (MMSE, range 0-30), somatic comorbidity, depression severity, and medication use. The total number of self-reported chronic diseases as determined by well-validated algorithms (Kriegsman et al., 1996) (lung disease, cardiovascular disease, diabetes mellitus, osteoarthritis or rheumatic disease, cancer, ulcer, intestinal problems, liver disease, epilepsy, and thyroid gland disease) was included. Severity of depression was measured using the 30-item self-rating Inventory of Depressive

Symptomatology (IDS) (Rush et al., 1996). Finally, antidepressant drug use as well as anti-inflammatory drugs (amino salicylic acid and similar agents, antiallergic agents, systemically applied co*rticosteroids, anti*-inflammatory and antirheumatic products, other analgesics and antipyretics, statins) drug use was controlled for.

Data analysis - Multiple linear regression analyses were conducted to examine the association between the different measures of physical frailty (independent variable) and each inflammatory marker (dependent variable) separately adjusted for all covariates described above. Because CRP and IL-6 values were positively skewed, ln-transformed values were used in all analyses.

The different measures of physical frailty included the presence of the physical frailty phenotype (yes/no), the number of the individual frailty criteria met (sum score), and five criteria (yes/no) individually. Associations with gait speed and handgrip strength (as two continuous proxies for frailty) were subsequently examined.

Finally, a non-linear principal components analysis (PCA) was conducted on the five binary criteria of the Fried Frailty Index (FFI). The purpose of PCA is data reduction. In PCA, relations between variables (in this case, the five FFI criteria) are analyzed, and underlying common factors are defined. So, factors are broadly formulated features that cover more than one variable (Cotteleer et al., 2003). PCA was chosen over factor analysis as PCA results in continuous latent factors (rotated axes) with purely binary variables (unrotated axes). Factor scores were calculated on the basis of unstandardized item factor loadings, the five criteria of the FFI in this case, and transformed into standardized z scores (using the Anderson-Rubin method) to increase their interpretability (Costello & Osborne, 2005).

Results

Sample - Of the 378 older persons with depression, three were excluded because they had missing values for one of the frailty criteria. Another nine were excluded due to missing data on all inflammatory markers because they refused or failed blood withdrawal. The mean age of the remaining 366 patients was 70.8 ± 7.4, and 242 (66.1%) were female. Table 1 presents the characteristics the study population for frail (n=97, 26.5%) and non-frail participants separately.

Table 1 Characteristics of the Study Population According to Frailty Status

Characteristic	Frail (N=97)	Non-frail (N=269)	P Value
Sociodemographic			
• Age, mean ± SD	74.0 ± 8.0	69.4 ± 6.7	<.001[b]
• Female sex, n (%)	68 (70.1)	174 (64.7)	.33[c]
• Education, years, mean ± SD	10.0 (3.2)	10.8 (3.5)	.01[b]
Somatic and cognitive functioning			
• Mini-Mental State Examination score, mean ± SD	27.3 ± 2.3	28.0 ± 1.7	.003[b]
• Number of somatic diseases, mean ± SD	2.6 ± 1.7	1.9 ± 1.4	<.001[b]
Use of medication, n (%)[a]			
• Antidepressant	76 (78.4)	189 (70.3)	.13[c]
• SSRI	29 (29.9)	70(26.0)	.47[c]
• TCA	33 (34.0)	56 (20.8)	.71[c]
• Other	33 (34.0)	72 (26.8)	.16[c]
• Anti-inflammatory	12 (12.4)	32 (11.9)	.90[c]
• Statin	27 (27.8)	59 (21.9)	.24[c]
Lifestyle characteristics			
• Current smoker, n (%)	22 (22.7)	73 (27.1)	.44[c]
• Alcohol use, n (%)			.08[c]
○ No	44 (45.4)	100 (37.2)	
○ Moderate	45 (46.4)	138 (51.3)	
○ Severe	4 (4.1)	29 (10.8)	
• Physical activity (metabolic equivalent minutes), mean ± SD	1,099.9 ± 1,497	2,884.8 ± 2,519.9	<.001[b]
• Body Mass Index, kg/m^2, mean ± SD	26.8 ±4.8	26.1 ± 4.1	.14[b]
Depression			
• Inventory of Depressive Symptoms sum score, mean ± SD	36.3 ± 12.0	27.4 ± 12.0	<.001[b]
• Late-onset depression, n (%)	33 (34.0)	79 (29.4)	.40[c]

Characteristic	Frail (N=97)	Non-frail (N=269)	P Value
Frailty			
• Fried Frailty Index, mean ± SD	3.4 ± 0.6	1.1 ± 0.8	<.001[b]
• Handgrip Strength, kg, mean ± SD	19.9 ± 8.8	30.6 ± 10.8	<.001[b]
• Gait speed, seconds, median (IQR)	9.0 (7.0)	6.4 (2.0)	<.001[d]
Inflammatory markers			
• C-reactive protein, mg/L, median (IQR)	2.20 (5.05)	1.87 (4.76)	.26[d]
• Interleukin-6 ,pg/L, median (IQR)	0.56 (10.80)	0.46 (5.64)	.17[d]
• Neutrophil gelatinase-associated lipocalin, ng/ml, mean ± SD	68.4 ± 26.5	59.9 ± 21.3	.01[b]

[a] Medications were defined according to the Anatomical Therapeutic Chemical classification system: selective serotonin reuptake inhibitor (SSRI) (N06AB), serotonin-norepinephrine reuptake inhibitor (N06AX16, N06AX21), tricyclic antidepressant (TCA)(N06AA) tetracyclic antidepressant (N06AX03, N06AX05, N06AX11), anti-inflammatory drug (including amino salicylic acid and similar agents) (A07EC), antiallergic agents (A07EB), systemically applied *corticosteroids* (H02A), *anti*-inflammatory and antirheumatic products (M01) and other analgesics and antipyretics (N02B), and statins (C10AA, C10B).
P-values were calculated using [b]t-tests, [c]chi-square tests, or [d]Mann-Whitney-U tests.
SD= standard deviation; IQR= interquartile range.

IL-6 levels were available for all patients, whereas CRP levels were missing for four and NGAL levels for one because of invalid laboratory results. CRP level was significantly associated with IL-6 (r=0.24, p<.001) and NGAL level (r=0.20, p<.001), whereas Il-6 and NGAL levels were not associated (r=0.04, p=.46). The severity of depressive symptoms (IDS sum score) was not associated with any of the inflammatory markers (CRP: Pearson correlation coefficient (r)=0.01, p=.83; IL-6: r<0.01, p=.94; NGAL: r=0.04, p=.50).

Association between inflammatory markers and the physical frailty phenotype – Bivariate and multivariate associations between inflammatory markers and the physical frailty phenotype are shown in table 2. In the fully adjusted models, only handgrip strength and gait speed were significantly associated with inflammatory markers (handgrip strength with CRP and IL-6, gait speed with NGAL).

Table 2 Associations Between C-Reactive Protein (CRP), Interleukin-6 (IL)-6, and Neutrophil Gelatinase-Associated Lipocalin (NGAL) and the Physical Frailty Phenotype

	CRP	IL-6	NGAL
Frailty Characteristics		**β (P Value)**	
Unadjusted			
• Frailty (0=no, 1=yes)	0.06 (.26)	0.05 (.36)	0.13 (.01)
• Frailty sum score (range 0 - 5)	0.10 (.055)	0.08 (.13)	0.20 (<.001)
Individual frailty criteria (dichotomous)			
• Weight loss	-0.03 (.53)	-0.02 (.71)	-0.03 (.56)
• Weakness	0.15 (.004)	0.12 (.02)	0.10 (.06)
• Exhaustion, poor energy	0.02 (.77)	-0.02 (.78)	0.11 (.04)
• Slowness	0.15 (.005)	0.11 (.04)	0.26 (<.001)
• Low activity level	<0.01 (.95)	0.03 (.64)	0.12 (.03)
Performance-based criteria (dimensional)			
• Handgrip strength	-0.13 (.01)	0.15 (.004)	-0.08 (.14)
• Gait speed	0.13 (.01)	0.12 (.03)	0.24 (<.001)
Fully adjusted[a]			
• Frailty (0=no, 1=yes)	0.04 (.56)	0.04 (.47)	0.02 (.73)
• Frailty sum score (range 0 - 5)	0.10 (.13)	0.08 (.21)	0.10 (.12)
Individual frailty criteria (dichotomous)			
• Weight loss	<0.01 (.99)	-0.03 (.64)	-0.07 (.20)
• Weakness	0.12 (.03)	0.09 (.10)	0.03 (.61)
• Exhaustion, poor energy	-0.01 (.91)	<-0.01 (.95)	0.07 (.23)
• Slowness	0.11 (.08)	0.08 (.22)	0.17 (.006)
• Low activity level	<-0.01 (.95)	0.06 (.39)	0.06 (.38)
Performance based criteria (dimensional)			
• Handgrip strength	-0.21 (.002)	-0.25 (<.001)	-0.04 (.57)
• Gait speed	0.09 (.18)	0.11 (.12)	0.15 (.02)

[a] Adjusted for age, sex, years of education, severity of depressive symptoms (Inventory of Depressive Symptomatology sum score), cognitive functioning (Mini Mental State Examination score), number of chronic diseases, anti-inflammatory drug use (including statins), antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, other), alcohol use (none, moderate, severe), smoking (yes/no), body mass index, physical activity (metabolic equivalent minutes).

Principal component analysis of physical frailty criteria - The scree plot of eigenvalues and the number of complex items revealed a two-factor solution as the optimal solution (KMO-measure of sampling adequacy: .575; Bartlett's test of sphericity: chi-square=50.1, degrees of freedom=10, p<.001). Handgrip strength, gait speed and

low activity level loaded on Factor 1 (explained variance: 28.7%, factor loadings 0.75, 0.65 and 0.55, respectively); this dimension was called 'performance-based physical frailty'. Weight loss and exhaustion loaded on Factor 2; this dimension was labeled 'vitality-based physical frailty' (explained variance: 20.2%, factor loadings 0.84 and -0.54, respectively).

The frailty dimensions did not correlate with each other (r=-0.08, p=.13). Associations between each dimension of physical frailty and the three inflammatory markers are shown in table 3.

Table 3 Associations Between C-Reactive Protein (CRP), Interleukin-6 (IL)-6 and Neutrophil Gelatinase Associated Lipocalin (NGAL) and Dimensions of the Physical Frailty Phenotype

Physical Frailty	CRP	IL-6	NGAL
		β (P Value)	
Unadjusted			
• Performance based	0.14 (.01)	.11 (.06)	.16 (.003)
• Vitality based	-0.03 (.56)	-.01 (.89)	-.09 (.07)
Fully adjusted[a]			
• Performance based	0.14 (.03)	.13 (.06)	.14 (.03)
• Vitality based	0.01 (.93)	-.02 (.69)	-.10 (.07)

[a] Adjusted for age, sex, years of education, severity of depressive symptoms (Inventory of Depressive Symptomatology sum score), cognitive functioning (Mini Mental State Examination score), number of chronic diseases, anti-inflammatory drug use (including statins), alcohol use (none, moderate, severe), smoking (yes/no), body mass index, physical activity (metabolic equivalent minutes).

Discussion

Main findings - The physical frailty phenotype was not associated with high levels of inflammatory markers in older adults with depression participating in the NESDO study. Nonetheless, performance-based measures such as handgrip strength and gait speed were associated with markers of low-grade inflammation. The criteria of the FFI represent two dimensions of physical frailty in a population with depression. Only one dimension, including the criteria based on the handgrip strength and gait

speed, was associated with inflammation independent of somatic illnesses, medication use or lifestyle characteristics.

Physical frailty phenotype in late-life depression - This first dimension, based on the criteria for weakness, slowness and low activity level, was called "performance-based physical frailty". Weight loss and exhaustion represented a second dimension, called "vitality-based physical frailty".

Measures of handgrip strength and gait speed are often used as indicators of sarcopenia (Fielding et al., 2011), which is considered to be an important mechanism underlying physical frailty (Evans 1997). The physical frailty criteria of exhaustion and of low physical activity may also be indicators of sarcopenia, but their relationship with sarcopenia is not straightforward. The physical frailty criterion of exhaustion may simply reflect a symptom of depression in the current sample for two reasons. First, this criterion is derived from a self-report instrument assessing depression severity (Radloff, 1977) and overlaps with the DSM-IV criteria for major depressive disorder. Second, exhaustion has many different causes in old age, of which sarcopenia is only one, among others such as anemia, endocrine disorders, sleep disorders, pain and polypharmacy.

The frailty component of low physical activity can be cause and consequence of depression or sarcopenia. Because low physical activity loads on the same dimension as handgrip strength and gait speed, it seems to reflect sarcopenia the current study population.

Finally, unintended weight loss may reflect sarcopenia but again, in the current study population probably, may be more likely a symptom of depression. Therefore, the dimension of vitality-based physical frailty has face validity for being a marker of depression severity instead of a true (second) dimension of physical frailty. Nonetheless, this hypothesis needs further validation.

Inflammation and frailty in late-life depression - Although the physical frailty phenotype was not associated with any of the three inflammatory markers, IL-6 and CRP were significantly associated with handgrip strength and NGAL with gait speed. These findings suggest differential patterns between specific inflammatory markers and specific frailty criteria. Nonetheless, all three inflammatory markers were associated with the performance-based physical frailty dimension. Low-grade inflammation may thus be a general mechanism underlying performance-based physical frailty.

The association between NGAL and vitality-based physical frailty is also of interest. In the NESDO study, only NGAL levels were higher in participants with depression than in those without (Naudé et al., 2014). NGAL seems to be an inflammatory marker associated not only with frailty in depression, but also specifically with depression.

Associations between high IL-6 and CRP levels and depression have not been found consistently (Ford & Erlinger, 2004; Dowlati et al., 2010). It might be that low-grade inflammation in depression is conditional on the level of frailty in the population under study, but this needs further investigation.

Methodological considerations - Strengths of the current study are the large number of older persons with depression and the comprehensive assessment of depression characteristics and confounding factors. However, some limitations should also be acknowledged. First, the cross-sectional study design precludes causal interpretations. It is generally assumed that depressive symptoms and frailty are reciprocally associated (Mezuk et al., 2012). Low-grade inflammation might be involved in both directions. Frailty-associated inflammatory processes may drive the pathway from frailty to depression by activating the hypothalamo-pituitary-adrenocortical axis (Schiepers et al., 2005; Bremmer et al., 2008). Conversely, low physical activity and low protein intake due to a depressive disorder may result in

sarcopenia, which in itself is associated with inflammation (Visser et al., 2002) and may culminate in the physical frailty phenotype. Longitudinal studies with repeated measurement of physical frailty, depression and inflammatory markers should be conducted to evaluate the sequence of events. Second, although negative cognitions (e.g. self-report symptoms of physical functioning) do not negatively bias performance-based measures of physical frailty, poorer performance due to lack of motivation during testing cannot be fully excluded, although research assistants were specifically trained to enhance motivation and performance as much as possible.

Conclusion - The operationalization of the physical frailty phenotype should be adapted in an older population with depression, with a more prominent role for criteria associated with low-grade inflammation that does not overlap with the criteria of depressive disorder. An interesting question that merits further investigation is to examine whether late-life depression with physical frailty represents a specific depressive subtype.

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