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Physical frailty and cognitive function among men with cardiovascular disease

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ABSTRACT

Aims: To assess the relationship between physical frailty and cognitive function among elderly men with a history of cardiovascular disease (CVD).

Methods: Three-hundred-twenty-four community-dwelling men with chronic CVD (mean age 77.2 ± 6.4 years) who previously participated in the Bezafibrate Infarction Prevention (BIP) trial (1990–1998) underwent assessment of frailty and cognitive function between 2011 and 2013. Physical frailty was assessed using the Fried phenotypic model, and cognitive performance overall and in memory, executive function, visuospatial and attention domains was evaluated using a validated set of computerized cognitive tests. Linear regression models were used to assess the cross-sectional relationship of frailty status and its components (gait speed, grip strength, weight loss, exhaustion and activity) with cognitive function overall and in specific domains, adjusting for age, education, smoking status, physical activity, history of myocardial infarction, hypertension, diabetes and dyslipidemia, systolic blood pressure, BMI and depression.

Results: Of the 324 men, 91 (28%) were frail and 121 (37%) were pre-frail. After controlling for potential confounders, severity of frailty was strongly associated with global cognitive function ($\beta = -8.0$, 95%CI $= -11.9, -4.1$ and $\beta = -3.3$, 95%CI $= -6.0, -0.5$ comparing frail and pre-frail to non-frail, respectively), with the most profound associations observed in executive function and attention. Gait speed was associated with overall cognitive performance and with all cognitive domains assessed in this study, and activity with none.

Conclusion: Cognitive function is poor among frail and pre-frail men with CVD, particularly in non-memory domains. Future research is warranted to address mechanisms and to assess the efficacy of interventions to improve physical and cognitive health.

1. Introduction

Frailty is a prevalent clinical condition among old adults, and is considered the most problematic expression of population aging (Clegg, Young, & Iliffe, 2013). It is defined as a state of increased vulnerability to sudden health status changes triggered by even a mild stressor event. While with aging there is a gradual decline in physiological reserve in multiple organ systems, among frail individuals the decline in reserves is accelerated and homeostasis starts to fail. As a consequence, there is a substantially higher risk of mortality, disability, falls and other adverse health problems associated with frailty (Clegg et al., 2013; Kojima, 2016).

Although the theoretical concept of frailty is quite accepted in the practical and research settings, there is still a debate regarding the role of cognitive impairment. Some evidence shows that cognitive function is only poorly correlated with frailty (Sourial, Bergman, & Karunananthan, 2012), and only 50% of individuals with Alzheimer's disease are also estimated to be frail (Bilotta, Bergamaschini, & Nicolini, 2012). Accordingly, frailty is widely defined using the phenotype model, which consists of five variables: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed and weak grip Strength. Yet, others postulate that cognitive impairment is one of the major contributors to the development of frailty and should be included in its assessment. There is good evidence from cross-sectional studies showing that prevalent frailty and cognitive impairment often coexist, and several underlying mechanisms for this link have been suggested (Halil, Cemal Kizilarslanoglu, & Emin Kuyumcu, 2015). In addition, some longitudinal studies show that frailty is a risk factor for cognitive decline (Buchman, Boyle, & Wilson, 2007; Samper-Ternent, Al Snih, & Raji, 2008a; Feng, Nyunt, & Gao, 2016), while

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others suggest that cognitive decline precedes frailty (Raji, Al Snih, & Ostir, 2010; Gross, Xue, & Bandeen-Roche, 2016).

Frailty and cardiovascular disease (CVD) are closely related: first, frailty is approximately 3 times more common in elderly with CVD compared to those without (von Haehling, Anker, & Doehner, 2013). Second, cardiac abnormalities demonstrate the greatest association with frailty compared to other organ systems (e.g. renal, pulmonary, adipose) (Nadruz et al., 2016). Third, frailty plays a role in CVD prognosis and outcomes (Singh, Stewart, & White, 2014) and its presence confers both high risk for and a consequence of CVD (Afilalo, Karunananthan, & Eisenberg, 2009). Importantly, findings point to a greater risk for vascular compared to Alzheimer's disease dementia subtype among frail compared to non-frail elderly (Solfrizzi, Scafato, & Frisardi, 2013; Avila-Funes, Carcaillon, & Helmer, 2012). In addition, some studies show that frailty is related more strongly to non-memory domains (Langlois, Vu, & Kergoat, 2012; Yassuda, Lopes, & Cachioni, 2012) hence implying a vascular pathology as an underlying mechanism, however other studies show associations with all cognitive domains (Robertson, Savva, Coen, & Kenny, 2014; Boyle, Buchman, & Wilson, 2010).

Disentangling the associations between frailty and cognition in individuals with CVD may shed light on the underlying mechanisms and may indicate causal pathways with potentially targets for interventions. Thus, our aim in the present study was to assess the relationship of frailty, pre-frailty and frailty individual components with cognitive performance overall and in specific cognitive domains among men with pre-existing cardiovascular disease.

2. Methods

2.1. Participants

This study includes participants who previously participated in a clinical trial of lipid modifications. This trial, the Bezafibrate Infarction Prevention (BIP) study, was a large multi-center, placebo-controlled randomized clinical trial investigating the efficacy of bezafibrate 400 mg daily, a fibric derivative, in secondary prevention among participants with established stable CVD (Bezafibrate Infarction Prevention (BIP) study, 2000). Participants were recruited from 18 medical centers in Israel between May 1990 and January 1993 and included men and women 45 to 74 years of age with a history of myocardial infarction at least 6 months and no longer than 5 years before enrollment and/or stable angina pectoris during the last 2 years confirmed by coronary angiography, and/or radionuclide studies or standard exercise tests. The lipid profile of participants at inclusion was as follows: serum total cholesterol 180 to 250 mg/dL, low-density lipoprotein–cholesterol $\leq$180 mg/dL ($\leq$160 mg/dL for people < 50 years), high-density lipoprotein–cholesterol $\leq$45 mg/dL, and triglycerides $\leq$300 mg/dL. Other exclusion criteria were insulin-dependent diabetes, hepatic or renal failure, and disabling stroke.

The sample for the current study consists of former participants of the BIP study, recruited from 8 medical centers located at the center of Israel, who subsequently participated in the BIP Neurocognitive study. As part of the neurocognitive study, these individuals underwent 2 follow-up evaluations, which included collection of data on health status and cognitive function (T1 and T2). The present study is based on data from the second evaluation, which was performed between the years 2011 and 2013 at the Sagol Neuroscience center, Sheba medical center, or at the participants' residence if he/she were unable or unwilling to arrive. Of the 363 participants who underwent the second evaluation, 39 subjects were excluded because they had a history of stroke. Since only 12 participants were females, we excluded them to allow a sample of only men. Thus, our final sample consisted of 324 individuals.

Data were obtained under a protocol approved by the institutional review board of the Sheba Medical Center and written informed consent was obtained from all participants.

2.2. Cognitive evaluation

Cognitive function was assessed using a comprehensive computerized battery (NeuroTrax Corp., Bellaire, TX). A description of the tests included has been published elsewhere (Dwolatzky, Whitehead, & Doniger, 2003). Several of these tests are based on common neuropsychological paradigms, including the Benton Visual Retention Test, Brief Visuospatial Memory Test, Tova, Stroop, and subsets of WAIS-III (Wechsler Adult Intelligence Scale, 3rd ed.) The psychometric properties of the tests exploit the advantages of computerized testing, providing precise accuracy and reaction time measurements. The tests are interactive and adaptive, adjusting the level of difficulty depending upon performance, and are designed for use with the elderly. Guidance and feedback were provided in the brief practice sessions that precede each test, but not during the actual tests. All responses were made using the mouse buttons or with the number pad on the keyboard.

2.3. Assessment of frailty

The Fried phenotypic definition of frailty was used (Fried, Tangen, & Walston, 2001). Participants were classified as frail if they met 3 or more of the following criteria: poor grip strength, slow gait speed, low levels of physical activity, unintentional weight loss, and exhaustion. Handgrip strength was tested using a hydraulic Jamar dynamometer (Sammons & Preston, Bolingbrook, IL,USA). Low grip strength was defined as $\leq$29 kg, $\leq$30 kg and $\leq$32 kg for individuals with body mass index (BMI) $\leq$24 kg/m^2, 24.1–28.0 kg/m^2 and > 28.0 kg/m^2, respectively. The test was carried out twice and the maximum score was recorded. For gait speed measurement, the participants were asked to walk at their usual pace along a 5-m line on the floor and the time taken to complete the task was recorded. Slow gait speed was defined as $\geq$6 s for those with bode height of $\leq$173 cm and $\geq$5 s for taller individuals (Fried et al., 2001).

Physical activity was assessed by the Physical Activity Scale for the Elderly scale (Samper-Ternent, Raji, Markides, & Ottenbacher, 2008b; Washburn, Smith, Jette, & Janney, 1993). Participants who scored in the lowest quintile were categorized as having low levels of physical activity. Unintentional weight loss was defined as a self- report of $\geq$4.0 kg loss of weight unintentionally in prior year. Lastly, exhaustion was assessed using two items from the Center for Epidemiological Studies Depression Scale (CES-D): (Radloff, 1977) (1) "I felt everything I did was an effort" or (2) "I could not get going". A response of "moderate amount of time (3–4 days)" or "most of the time (5–7days) last week" was classified as exhaustion.

2.4. Additional assessments

Data was collected systematically regarding new co-morbidities and hospitalizations, medication use, smoking status, physical activity, and anthropometric data. Stroke and dementia were assessed by an adjudication committee composed of 3 investigators, 2 of which were experienced board-certified neurologists who reviewed records from hospital or emergency department discharge, primary care physician, or neurologists. Stroke was defined according to the World Health Organization criteria (Hatano, 1976). Dementia was determined based on the sum of cognitive evaluation, clinical interview and data collected and in accordance with the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria (*Diagnostic and statistical manual of mental disorders*, 1994). Depression was assessed using a cut off of 5 on the Geriatric Depression Scale (Montorio & Izal, 1996).

2.5. Data analysis

Data were analyzed using SAS version 9.4. Chi-square tests and one-