JAMDA 18 (2017) 89.e1–89.e8

JAMDA

journal homepage: www.jamda.com

Original Study

Reversible Cognitive Frailty, Dementia, and All-Cause Mortality. The Italian Longitudinal Study on Aging

Vincenzo Solfrizzi MD, PhD [a,†], Emanuele Scafato MD [b], Davide Seripa PhD [c], Madia Lozupone MD [d], Bruno P. Imbimbo PhD [e], Angela D'Amato MD [a], Rosanna Tortelli MD [d], Andrea Schilardi MD [a], Lucia Galluzzo MD [b], Claudia Gandin MD [b], Marzia Baldereschi MD [f], Antonio Di Carlo MD [f], Domenico Inzitari MD [f,g], Antonio Daniele MD, PhD [h], Carlo Sabbà MD [a], Giancarlo Logroscino MD, PhD [d,i], Francesco Panza MD, PhD [c,d,i,*,†] on behalf of the Italian Longitudinal Study on Aging Working Group [‡]

[a] *Department of Geriatric Medicine, Memory Unit and Rare Disease Center, University of Bari Aldo Moro, Bari, Italy*
[b] *Population Health and Health Determinants Unit, National Center for Epidemiology, Surveillance and Health Promotion (CNESPS), Istituto Superiore di Sanità (ISS), Roma, Italy*
[c] *Gerontology-Geriatrics Research Laboratory, Istituto di Ricovero e Cura a Carattere Scientifico Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy*
[d] *Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy*
[e] *Research and Development Department, Chiesi Farmaceutici, Parma, Italy*
[f] *Institute of Neuroscience, Italian National Research Council (CNR), Firenze, Italy*
[g] *Department of NEUROFARBA, Neuroscience Section, University of Florence, Florence, Italy*
[h] *Institute of Neurology, Catholic University of Sacred Heart, Rome, Italy*
[i] *Department of Clinical Research in Neurology, University of Bari Aldo Moro, Pia Fondazione Cardinale G. Panico, Tricase, Lecce, Italy*

Keywords:
Frailty
cognitive aging
vascular dementia
Alzheimer disease
dementia
mortality

A B S T R A C T

Objectives: Cognitive frailty, a condition describing the simultaneous presence of physical frailty and mild cognitive impairment, has been recently defined by an international consensus group. We estimated the predictive role of a "reversible" cognitive frailty model on incident dementia, its subtypes, and all-cause mortality in nondemented older individuals. We verified if vascular risk factors or depressive symptoms could modify this predictive role.
Design: Longitudinal population-based study with 3.5- and 7-year of median follow-up.
Setting: Eight Italian municipalities included in the Italian Longitudinal Study on Aging.
Participants: In 2150 older individuals from the Italian Longitudinal Study on Aging, we operationalized reversible cognitive frailty with the presence of physical frailty and pre-mild cognitive impairment subjective cognitive decline, diagnosed with a self-report measure based on item 14 of the Geriatric Depression Scale.
Measurements: Incidence of dementia, its subtypes, and all-cause mortality.
Results: Over a 3.5-year follow-up, participants with reversible cognitive frailty showed an increased risk of overall dementia [hazard ratio (HR) 2.30, 95% confidence interval (CI) 1.02–5.18], particularly vascular dementia (VaD), and all-cause mortality (HR 1.74, 95% CI 1.07–2.83). Over a 7-year follow-up, participants with reversible cognitive frailty showed an increased risk of overall dementia (HR 2.12, 95% CI 1.12–4.03), particularly VaD, and all-cause mortality (HR 1.39, 95% CI 1.03–2.00). Vascular risk factors and depressive symptoms did not have any effect modifier on the relationship between reversible cognitive frailty and incident dementia and all-cause mortality.
Conclusions: A model of reversible cognitive frailty was a short- and long-term predictor of all-cause mortality and overall dementia, particularly VaD. The absence of vascular risk factors and depressive symptoms did not modify the predictive role of reversible cognitive frailty on these outcomes.

* Address correspondence to Francesco Panza, MD, PhD, Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy and Geriatric Unit and Gerontology-Geriatric Research Laboratory, IRCCS Casa Sollievo della Sofferenza, Viale Cappuccini 1, 71013 San Giovanni Rotondo, Foggia, Italy

E-mail address: geriat.dot@geriatria.uniba.it (F. Panza).

† These 2 authors contributed equally to this work.

‡ A list of members of Italian Longitudinal Study on Aging Working Group is available in the Appendix.

http://dx.doi.org/10.1016/j.jamda.2016.10.012
1525-8610/

Frailty is a geriatric syndrome reflecting a nonspecific state of vulnerability and a multisystem physiological change.[1] Physical frailty[1] or frailty indexes with a multidimensional nature[2] are associated with a greater risk for adverse health-related outcomes (falls, disability, hospitalization, institutionalization, and death)[1,2] or cognitive-related outcomes (dementia and late-life cognitive disorders).[3] In particular, a very recent systematic review and meta-analysis suggested that physical frailty defined by Cardiovascular Health Study criteria[1] was a significant predictor of Alzheimer disease (AD), vascular dementia (VaD), and all dementia among community-dwelling older people, with frail women that may have a higher risk of incident AD than frail men.[4] In 2013, an international consensus group from the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics (IANA/IAGG) defined cognitive frailty[5] as a heterogeneous clinical condition characterized by the simultaneous presence of both physical frailty and cognitive impairment and the exclusion of concurrent AD or other dementias.[6] At present, some longitudinal population-based studies investigated cognitive frailty models associated with increased disability and all-cause mortality.[7–10]

In an attempt to refine the framework for the definition and potential mechanisms of cognitive frailty, Ruan et al[11] proposed 2 subtypes for this clinical construct: "potentially reversible" cognitive frailty and "reversible" cognitive frailty. The physical factors should be physical prefrailty or frailty for both the subtypes.[3,11] The cognitive impairment of potentially reversible cognitive frailty should be mild cognitive impairment (MCI) [Clinical Dementia Rating scale (CDR) = 0.5], as proposed by the IANA/IAGG consensus group,[6] whereas the cognitive impairment of reversible cognitive frailty should be pre-MCI subjective cognitive decline (SCD), as recently formulated by the SCD Initiative (SCD-I) Working Group that proposed a basic conceptual framework for the study of the common concepts of SCD, pre-MCI SCD, and SCD in preclinical AD.[12] SCD is a nonspecific condition that may appear as the first symptom of preclinical AD (the asymptomatic at-risk stage of AD or pre-MCI stage of patients with AD), also emerging in patients with various types of pre-MCI.[12] Therefore, among cognitive frailty models, the proposed definition of reversible cognitive frailty could be an interesting further step toward the identification of a reversible target for this new clinical entity.[3,11] At present, there is no population-based study in which reversible cognitive frailty has been investigated as a possible determinant of dementia and its subtypes and all-cause mortality as well how mechanisms could be associated with reversibility. Probably, the identification of reversibility because of several possible interventions could be more useful in designing randomized clinical trials (ie, the multidomain preventive trials of cognitive decline and dementia, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability).[13] However, in observational studies such as the present study, in extreme cases, it could be of interest to verify that an interaction may reverse the relationship between the risk factor and the outcome. Therefore, it was hypothesized that the role of vascular factors and/or depressive symptoms as effect modifiers could modify the risk of dementia and all-cause mortality linked to the presence of reversible cognitive frailty. In particular, we focused on the group of people without these risk factors as a proxy of optimal management of these factors. In the present study, we explored the hypothesis that reversible cognitive frailty was associated with a greater risk of developing dementia and its subtypes and all-cause mortality in a large population-based sample of older individuals without cognitive impairment. Moreover, trying to support the reversibility of this new clinical construct, we verified if the absence of vascular risk factors or depressive symptoms could have a role in reversing the relationship between reversible cognitive frailty and these outcomes.

Methods

Setting

The participants of this study were enrolled in a large population-based study, the ILSA.[14] A sample of 5632 individuals aged 65–84 years old, independent or institutionalized, was randomly selected from the electoral rolls of 8 Italian municipalities, after stratification for age and sex. The data of the present study have been obtained during the first prevalence survey study between March 1992 and June 1993, the second prevalence survey study between September 1995 and October 1996, and the third prevalence survey between March 2000 and September 2001. The study project was approved by the Institutional Review Board of the 8 municipalities of the Italian Longitudinal Study on Aging. Informed consent was obtained from each participant and/or their relatives before enrollment.

Clinical Examination and Laboratory Analyses

Cases of coronary artery disease (CAD) (myocardial infarction or angina pectoris), congestive heart failure (CHF), type 2 diabetes mellitus (T2DM), hypertension, and stroke were identified with a 2-phase procedure, using clinical criteria described in detail elsewhere.[14] Based on self-reports, smoking habits were categorized as "ever" or "never," and the variable "pack-years cigarettes" (years smoked × usual number of cigarettes smoked/20 cigarettes per pack) was generated to represent the total smoking exposure. Body mass index was calculated as weight/height^2 (kg/m^2). Functional status was assessed with the activities of daily living (ADL) scale,[15] whereas ability in home management was assessed by the instrumental activities of daily living (IADL) scale.[16] Mini-Mental State Examination (MMSE) was used to evaluate global cognitive function.[17] Episodic memory was tested with the Babcock Story Recall Test[18] and selective attention was assessed by the Digit Cancellation Test.[18] Depressive symptoms were investigated using the Italian version of the Geriatric Depression Scale (GDS)-30 items.[19] The physical activity practice was assessed by the administration of a structured questionnaire specifically developed for the InChianti Study.[20] Motor-performance was assessed using the 6 tests of a battery designed to measure motor ability in older people.[21] The Charlson comorbidity index, a weighted index that takes into account the number and the seriousness of comorbid disease, was calculated.[22] Data on vital status were gathered directly from study participants or proxy responders. Death certificates were collected for those who died. The date and cause of death for all participants who died were obtained from death certificates and other official sources, and trained physicians coded the cause of death according to the *International Classification of Disease, 9th Revision*. Serum albumin was measured by electrophoresis, as detailed elsewhere.[23]

Classification of Dementia

The case finding strategy for the diagnosis of dementia was described in detail elsewhere.[14] Briefly, the diagnosis was based on the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised* criteria for dementia syndrome,[24] the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria for possible and probable AD,[25] the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* criteria for VaD, and other dementing diseases.[26] We used diagnostic criteria for MCI defined by Petersen et al,[27] and detailed elsewhere.[14]