

# Additive Role of a Potentially Reversible Cognitive Frailty Model and Inflammatory State on the Risk of Disability: The Italian Longitudinal Study on Aging

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**Objective:** Cognitive frailty is a condition recently defined by operationalized criteria describing the simultaneous presence of physical frailty and mild cognitive impairment (MCI). Two subtypes for this clinical construct have been proposed: “potentially reversible” cognitive frailty (physical frailty plus MCI) and “reversible” cognitive frailty (physical frailty plus pre-MCI subjective cognitive decline). Here the prevalence of a potentially reversible cognitive frailty model was estimated. It was also evaluated if introducing a diagnosis of MCI in older subjects with physical frailty could have an additive role on the risk of dementia, disability, and all-cause mortality in comparison with frailty state or MCI condition alone, with analyses separately performed for inflammatory state. **Methods:** In 2,373 individuals from the population-based Italian Longitudinal Study on Aging with a 3.5-year-follow-up, we operationally categorized older individuals without dementia into four groups: non-frail/non-MCI, non-frail/MCI, frail/non-MCI, and frail/MCI. **Results:** The prevalence of potentially reversible cognitive frailty was 1%, increasing with age and more represented in women

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than in men, and all groups were associated with significant increased incident rate ratios of dementia, disability, and mortality. A significant difference in rates of disability has been found between the MCI and non-MCI groups (contrasts of adjusted predictions: 0.461; 95% confidence interval: 0.187–0.735) in frail individuals with high inflammatory states (fibrinogen >339 mg/dL). **Conclusion:** In older individuals without dementia and with elevated inflammation, a potentially reversible cognitive frailty model could have a significant additional predictive effect on the risk of disability than the single conditions of frailty or MCI. (Am J Geriatr Psychiatry 2017; ■■■:■■■–■■■)

**Key Words:** Frailty, cognitive aging, Alzheimer disease, disablement process, inflammation, lifestyle

### Highlights

- Cognitive frailty described coexisting physical frailty and cognitive impairment in nondemented older subjects.
- Two subtypes have been proposed: “potentially reversible” cognitive frailty [physical frailty plus mild cognitive impairment (MCI)] and “reversible” cognitive frailty (physical frailty plus pre-MCI subjective cognitive decline).
- The prevalence of potentially reversible cognitive frailty was 1 %, with all groups associated to increased incident rate ratios of dementia, disability, and mortality.
- A significant difference in disability rates existed between the MCI and non-MCI groups in frail individuals with high inflammation.
- With inflammation, a potentially reversible cognitive frailty model may have an additional predictive effect on the disability risk than frailty or MCI alone.

## INTRODUCTION

Among age-related conditions strictly linked to Alzheimer disease (AD) and late-life cognitive disorders, frailty is a multidimensional geriatric syndrome reflecting a nonspecific state of vulnerability and a multisystem physiologic change.<sup>1</sup> Both physical, biologic, or phenotypic frailty and frailty indices with a multidimensional nature are generally associated with a greater risk for adverse health-related outcomes (falls, disability, hospitalization, institutionalization, and death)<sup>1,2</sup> or adverse cognitive-related outcomes (delirium and late-life cognitive disorders).<sup>3–5</sup> In particular, physical frailty may be linked to cognitive impairment,<sup>6</sup> incident AD,<sup>7</sup> mild cognitive impairment (MCI),<sup>8</sup> vascular dementia (VaD),<sup>9</sup> non-AD dementias,<sup>10</sup> and AD pathology.<sup>11</sup> Recently, a meta-analysis suggested that physical frailty was a significant predictor of AD, VaD, and all dementia among community-dwelling older people, with frail women at higher risk of incident AD than frail men.<sup>12</sup>

On this basis, 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” as a heterogeneous clinical condition characterized by the simultaneous presence of both physical frailty and cognitive impairment and exclusion of concurrent AD or other dementias.<sup>13</sup> In an attempt to refine the framework for the definition and potential mechanisms of cognitive frailty, Ruan et al.<sup>14</sup> proposed two subtypes for this clinical construct: “potentially reversible” cognitive frailty and “reversible” cognitive frailty. The physical factors should be physical prefrailty or frailty for both subtypes.<sup>5,14</sup> The cognitive impairment of potentially reversible cognitive frailty should be MCI (Clinical Dementia Rating scale [CDR] = 0.5), as proposed by the IANA/IAGG consensus group,<sup>13</sup> whereas the cognitive impairment of reversible cognitive frailty should be pre-MCI subjective cognitive decline (SCD), as formulated by the SCD Initiative Working Group, which proposed a basic conceptual framework for the study of the common concepts of SCD, pre-MCI SCD, and SCD in preclinical AD.<sup>15</sup> SCD is a nonspecific condition that may appear as the first symptom of preclinical AD (the asymptomatic at-risk stage of AD

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