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RESEARCH ARTICLE

# Biopsychosocial frailty and mild cognitive impairment subtypes: Findings from the Italian project on the epidemiology of Alzheimer's disease (IPREA)

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## Abstract

**Introduction:** Frailty is a critical intermediate status of the aging process including physical, cognitive, and psychosocial phenotypes. We operationalized a biopsychosocial frailty construct, estimating its association with mild cognitive impairment (MCI) and its subtypes.

**Methods:** In 1980, older individuals from the population-based Italian PRoject on the Epidemiology of Alzheimer's disease (IPREA), we investigated cross-sectional associations among biopsychosocial frailty, MCI, and its subtypes.

**Results:** Participants with biopsychosocial frailty showed an increased odds ratio (OR) of MCI [OR: 4.36; 95% confidence interval (CI): 2.60-7.29; Fisher's exact $p < 0.01$], particularly for nonamnestic MCI single domain (naMCI-SD, OR:3.28; 95% CI: 1.35-7.97; Fisher's exact $p = 0.02$) and for nonamnestic MCI multiple domain (naMCI-MD, OR:6.92; 95% CI: 3.37-14.21; Fisher's exact $p < 0.01$). No statistically significant associations between amnestic MCI single or multiple domain and biopsychosocial frailty were observed.

**Discussion:** In a large, older Italian cohort, a biopsychosocial frailty phenotype was associated with MCI, in particular, could be associated with some of its subtypes, that is, naMCI-SD, and naMCI-MD.

Vincenzo Solfrizzi and Emanuele Scafato contributed equally to this work.

  

KEYWORDS
Alzheimer's disease, cognitive frailty, dementia, frailty, lifestyle, physical frailty, social frailty

## 1 | INTRODUCTION

Frailty is a homeostatic imbalance and functional decline in physiological reserves of systems exacerbate by multiple subclinical and age-related conditions and the occurrence of ageing stressors.[1] This critical intermediate status of the aging process can be defined as a unidimensional entity, mainly based on the physical or biological dimension,[2] or as a non-specific multidimensional status based on a deficit accumulation model.[3] Given its multidimensional nature, frailty could include physical,[2] social,[4] cognitive,[5] sensorial,[6] psychological,[5] and nutritional[7] domains or phenotypes, which need to be accounted for in its definition, management, and prevention. Frail older people were at higher risk for adverse health-related outcomes, including falls, disability, hospitalizations, mortality, and dementia.[8] In particular, these frailty phenotypes may also represent a precursor of neurodegenerative processes and Alzheimer's disease (AD) and involve them in the earliest intervention which should be taken into account for a potential reversibility.[5,8] In fact, different frailty phenotypes were associated with late-life cognitive impairment/decline, incident dementia, AD, mild cognitive impairment (MCI), vascular dementia (VaD), non-AD dementias, and AD pathology.[5]

Among these proposed frailty phenotypes, the biopsychosocial frailty construct, combining physical and psychosocial domains,[4,9] was based like the deficit accumulation model on the results of a previous comprehensive geriatric assessment (CGA),[10] defining a status of biological aging and including cognitive, emotional, motivational, and social characteristics. Biopsychosocial frailty may add important value in both assessment and target of intervention during frailty. In fact, previous findings from the Italian Longitudinal Study on Aging (ILSA) suggested that over a 3.5- and 7-year follow-ups, participants with biopsychosocial frailty showed an increased risk of overall dementia, particularly VaD.[4] We hypothesized that also MCI may be an outcome of the biopsychosocial frailty, that is, examining the risk of MCI that in frail older adults may be increased. In the present report, using data from the population-based Italian PRoject on the Epidemiology of Alzheimer's disease (IPREA), we investigated if the operationalization for a biopsychosocial frailty construct developed in the ILSA may be associated with MCI and its subtypes.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population and sample size

The IPREA was coordinated by the Istituto Superiore di Sanità in Rome (Italian National Health Institute) and the study design and methodology have been described in detail elsewhere.[11] The study sample consisted of 4785 individuals aged 65 to 84 years living at home or institutionalized, stratified by gender and 5-year age group. The sample was randomly selected from the registers of 12 municipalities in 12 Italian regions (400 persons of each of the 12 participating cities and towns, 50 males and 50 females for four age groups: 65 to 69, 70 to 74, 75 to 79, 80 to 84 years), including both rural and urban areas according to strategy of a stratified by equal allocation randomization (Figure 1). Although we had expected to select 4800 individuals, this was not possible because an earthquake occurred in one of the operative units (Larino), resulting in a massive evacuation and change of residence especially for the oldest group of individuals. We selected Local Health Units (university clinics or national research institutes) on the basis of their previous experience in epidemiological studies on aging. We used the same eight Local Health Units of the ILSA project plus other 4 units.[12] The following criteria were used to choose the sample size: the total budget was considered sufficient to make a survey on about 4000 subjects; assuming a priori a participation rate equal to 80%, the number of sampled subjects should be of about 4800 individuals; if these 4800 individuals should be a random sample of the Italian population, aged 65 to 84 years, the study would allow estimating a prevalence of 5% with a standard error ±0.7, a prevalence of 10% with an error ±0.9, a prevalence of 20% with an error ±1.3; these values of standard errors were considered satisfactory; the equal allocation strategy in each stratum was adopted because the standard errors of estimates were lower than those obtained with a proportional strategy. Moreover, a proportional strategy in this population would select a decreasing number of subject in the older classes, (where also the participation was expected to decrease), and a lower number of men versus the number of women. Thus, we adopted an equal allocation strategy by gender and age groups in order to obtain solid number even in the highest age group. We excluded individuals with the following conditions: clinically severe impairment in hearing, visual acuity, or language; mental retardation or psychoses; severe or terminal diseases; severe dementia (including AD) already diagnosed at the time of the enrolment. We used the Clinical Dementia Rating Scale (CDR) for staging the demented patients, excluding those with a CDR = 3 at the time of the enrolment (CDR Assessment Protocol Italian certified translation—https://knightadrc.wustl.edu/wp-content/uploads/2021/10/Italian-Italy.pdf).[13,14] The cross-sectional phase was carried out between June 2003 and May 2004.

### 2.2 | Cross sectional survey

#### 2.2.1 | Baseline screening phase

The study candidates received a letter explaining the study aims and inviting them to participate, then, they were contacted by telephone. All participants were required to provide written informed

**RESEARCH IN CONTEXT**

1. **Systematic review**: We searched electronic databases (e.g., PubMed, Embase, Scopus, and Web of Science) for both cross-sectional and longitudinal studies published in English, from database inception to December 18, 2022, that provided a description of the diagnostic criteria used for the biopsychosocial frailty phenotype, mild cognitive impairment (MCI) and its subtypes, dementia, Alzheimer's disease (AD), and vascular dementia. In the present population-based study, we investigated if the operationalization for a biopsychosocial construct may be associated to MCI and its subtypes.
2. **Interpretation**: Different frailty phenotypes may be linked to dementia and late-life cognitive decline. To the best of our knowledge, this was the first population-based study that estimated the association of a biopsychosocial frailty model, a condition describing the simultaneous presence of physical and psychosocial frailty, with MCI and its subtypes in nondemented Italian older individuals. In the present large cohort, the prevalence rates of the biopsychosocial frailty phenotype and MCI were 7.1% and 5.1, respectively. Furthermore, this biopsychosocial frailty phenotype was associated with MCI and some of its subtypes, i.e., nonamnestic MCI single domain and nonamnestic MCI multiple domain.
3. **Future directions**: The present findings suggested that a modifiable risk factor such as a biopsychosocial frailty phenotype may be associated with late-life cognitive decline, i.e., MCI and its subtypes, particularly nonamnestic MCI. In the next few years, randomized clinical trials are needed to address whether preventing biopsychosocial frailty phenotype may also prevent MCI onset and its progression to overt dementia in healthy older individuals.

consent; for persons with dementia or severe cognitive impairment, the informed consent was obtained from relatives or caregivers. For those who refused to participate, information on level of education was, when possible, recorded. The screening phase consisted of a personal interview, medical and cognitive evaluation. The personal interview was conducted using a structured questionnaire at the local operative unit or the participant's home or institution of residence. It included information on socio-demographic characteristics, medical history, current medication, and risk factors for dementias and comorbidities.[11] The cognitive evaluation mainly consisted of the assessment of the five main cognitive domains included in the aging-associated cognitive decline (AACD) model, developed by the International Psychogeriatric Association (IPA) in collaboration with the World Health Organization.[15] The following neuropsychological tests, which were validated for the Italian population, were used: Buschke Fuld Selective Reminding Test[16] (memory and learning), Trail Making Test, A and B[17] (attention), Verbal Fluency Test for semantic categories[18] (verbal ability), Constructional Praxis[16] (visuoconstructive function), and Raven colored progressive matrices[19] (problem-solving). For each cognitive domain, the results were adjusted using age- and education-specific criteria. Test performances were defined abnormal when the score was at least 1 standard deviation (SD) below the mean value (specific for age and educational level) for the Italian population, as suggested by Levy.[15] The neuropsychological test battery also included the Mini-Mental State Examination (MMSE) to evaluate overall cognitive function: (orientation, attention, immediate and delayed verbal memory, constructional praxis and language),[20] the Memory Complaint Questionnaire (MAC-Q), assessing subjective memory complaint,[21] the Katz index of Activities of Daily Living (ADL), for basic functional status assessment,[22] the Lawton scale, for Instrumental Activities of Daily Living (IADL), evaluating ability in home management,[23] the 30-item Geriatric Depression Scale (GDS-30) to evaluate depressive symptoms,[24] the CDR, assessing the severity of dementia.[13,14] Information on subjective cognitive complaints other than memory (investigated using the MACQ) were collected from participants. Subsection H of CAMDEX was administered to informants to investigate participants' cognitive, behavioral and functional deficits.[25] Finally, additional questions were asked to the informants in order to obtain further information on behavioral deficits and cognitive complaints. Specific norms for gender, educational level, and age for Italians were taken into consideration, and all tests were standardized and validated using the Italian population as reference. Pack-years were evaluated by the (number of cigarettes smoked per day/20) × number of years smoked.

### 2.2.2 | Clinical confirmation phase and definitions of MCI and its subtypes

To confirm the diagnosis of dementia or of cognitive impairment without dementia and to perform differential diagnoses, a clinical and neuropsychological examination was conducted for participants with a CDR of ≥0.5, isolated memory impairment, memory impairment plus deficits of other cognitive domains, or deficits of other cognitive domains without memory impairment.[26] The diagnostic process was performed in the twelve IPREA centers by a single expert clinician (geriatrician or neurologist). We followed the core clinical criteria for individuals with MCI designed to be used in all clinical settings,[27,28] that is, cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time) evaluated by the MAC-Q test; objective cognitive impairment defined as a CDR of 0.5 which is a commonly-used criterion for MCI,[29] objective evidence of Impairment in one or more cognitive domains, typically including memory, in particular delayed recall (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) in the lowest 10th percentile of the distribution of age- and education-adjusted scores after exclusion

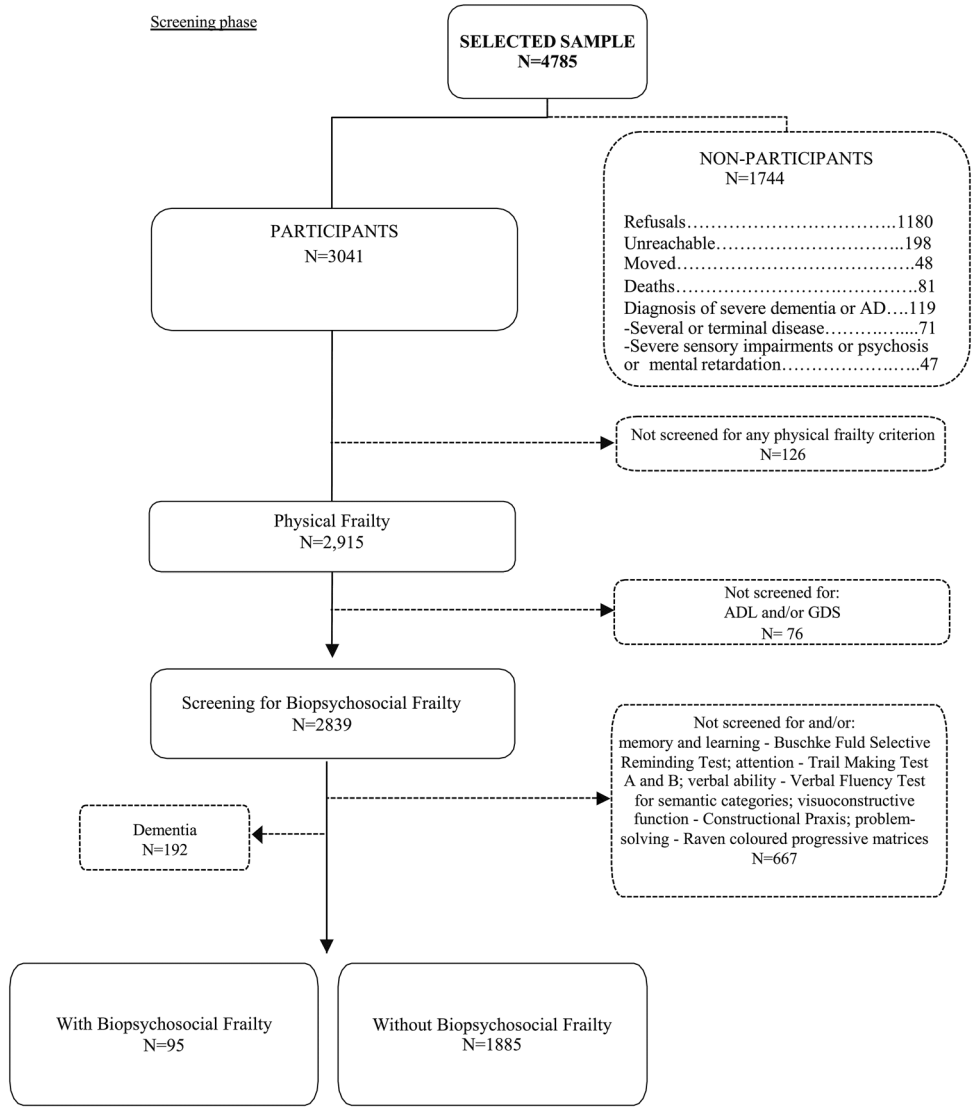


**FIGURE 1** Attrition of the study sample at the different phases of the survey for biopsychosocial frailty and mild cognitive impairment (MCI). Italian PRoject on the Epidemiology of Alzheimer's disease (IPREA). AD, Alzheimer's disease; GDS-30, 30-item Geriatric Depression Scale; ADL, activities of daily living

of prevalent dementia at entry; independence in the basic activities of daily living, as measured by ADL; not demented. The MCI subtypes [amnestic MCI single domain (aMCI-SD), amnestic MCI multiple domain (aMCI-MD), nonamnestic MCI single domain (naMCI-SD), and nonamnestic MCI multiple domain (naMCI-MD)] were diagnosed using the comprehensive neuropsychological test battery and the Petersen algorhytm.[30]

### 2.2.3 | Definitions of frailty: Physical and biopsychosocial phenotypes

A phenotype of physical frailty was operationalized slightly modifying the Cardiovascular Health Study criteria[2] and was identified by the presence of three or more frailty components: (1) weight loss, as unintentional weight loss > 5 kg in the last year; (2) self-reported exhaustion, identified by one question from the GDS-30 scale: "Do you feel full of energy?"; (3) weakness, as inability of standing on one leg without gait and balance disorders; (4) slowness, supported by the answers to the survey questionnaire dedicated to identify congestive heart failure symptoms: "Do you ever have to stop for shortness of breath while walking quickly on the flat or while slightly walking uphill?" and/or " Do you have to walk slower than people your own age due to shortness of breath?" and/or "Do you ever have to stop and breathe when walking at a normal pace on level ground?"; (5) low level of physical activity, using the physical activity questionnaire: inactive or light physical activity. To develop a biopsychosocial construct, the items of GDS-30 and IADL scales, instruments usually used in the CGA,[10] went through a qualitative judgment process, as reported elsewhere.[4] We considered the biopsychosocial frail older individuals, as previously defined physical frail individuals with at least one of the two GDS-30 items impaired (item 3:"Do you feel that your life is empty?"

or item 10:"Do you often feel helpless?") as biopsychosocial frail individuals.[4]

### 2.3 | Statistical analysis

The prevalence estimates of biopsychosocial frailty and MCI were based on baseline data collected in the IPREA survey. A poststratification adjustment by age and gender was used to make the sample consistent with the population represented. Prevalence punctual estimates and 95% confidence interval (CI) were evaluated according to the procedures of complex surveys supported by Stata package (The SVYSET command and the SVY: prefix) on the basis of the characteristics of the IPREA sampling. For quantitative variables, we used the t-test to compare means for two groups of cases, and the chi-square test to evaluate the relationship between two qualitative variables and we used the Mantel-Haenszel Test of Linear Association to evaluate linear trends by age groups and gender (*p* value evaluated with Fisher's exact test). Analyses were performed using Stata statistical software (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). The statistical significance threshold was set at 0.05.

## 3 | RESULTS

Of the 4785 subjects (mean age 74.0 ± 5.5 years) of the IPREA, 3278 were reached by telephone and they were enrolled in the study (response rate: 68.5%; 65.7% of women and 71.3% of men, $p < 0.01\%$) (Figure 1). Of the 1507 subjects not enrolled (mean age 74.9 ± 5.7 years), 1180 refused to be interviewed, 197 were unreachable, 48 were moved elsewhere, and 82 died before the interview could be conducted. Out of 3278 subjects, 237 were excluded (119 because of a pre-existing diagnosis of severe dementia or AD, 71 with a severe or terminal disease, and 47 with severe sensory impairment or psychosis or mental retardation). Thus, 3041 subjects were submitted to the personal interview and participated in the study, 0.5% of them were institutionalized. Of the 3041 persons interviewed, 2839 were screened for biopsychosocial frailty. Finally, 1980 older individuals were screened for MCI and for the biopsychosocial frailty phenotype (Figure 1).

### 3.1 | Sociodemographic and clinical characteristics

In the present study, the prevalence rate of biopsychosocial frailty amounted to 6.77% [95% confidence interval (CI): 5.83-7.87). It increased with class of age [Mantel–Haenszel estimate, odds ratio (OR): 2.82; 95% CI: 2.00-3.96], was higher in women than in men (Mantel–Haenszel estimate, OR: 2.47; 95% CI: 1.76-3.48), and increased with class of age indifferently in men and in women (Mantel–Haenszel estimate, OR: 2.54; 95% CI: 1.67-3.83 for women and Mantel–Haenszel estimate, OR: 3.68; 95% CI: 1.97-6.89 for men). Older individuals screened for biopsychosocial frailty were younger than the 2805 individuals not screened (72.27 ± 4.94 *vs.* 75.65 ± 5.65, $p < 0.001$, evaluated by separate variance t-test) and in the screening were involved more men than women [not screened: 1299 (54.31%) men and 1506 women (62.93%) and screened: 1093 (45.69%) men and 887 (37.07%) women (Pearson chi2: 36.71, $p < 0.001$)]. Among those screened, biopsychosocial frail individuals were older (75.54 ± 4.74 *vs.* 72.11 ± 4.89, $p < 0.001$), women were more numerous than men, less educated, more cognitively impaired, and with a greater multimorbidity than older individuals without biopsychosocial frailty (Table 1). Biopsychosocial frail individuals were also more depressed than older individuals without biopsychosocial frailty (Table 1).

### 3.2 | Estimates of prevalence of mild cognitive impairment and its subtypes

In the present population-based study, the prevalence rate of MCI was 8.23% (95% CI: 6.88-9.81). It increased with class of age [Mantel–Haenszel estimate, OR: 2.77; 95% CI: 1.96-3.92; $p < 0.001$], while no difference by gender was identified (Mantel–Haenszel estimate, OR: 1.30; 95% CI: 0.93-1.82; $p = 0.1301$). In this study population, the prevalence rate of aMCI-MD was 1.54% (95% CI: 1.07-2.21). It did not increase significantly with class of age (Mantel–Haenszel estimate, OR: 1.89; 95% CI: 0.96-3.72; $p = 0.063$) or in women than in men (Mantel–Haenszel estimate, OR:1.09; 95% CI: 0.55- 2.15; $p = 0.81$) (Table 2). In this study population, the prevalence rate of aMCI-SD was 1.39% (95% CI: 0.84-2.27). It increased significantly with class of age (Mantel–Haenszel estimate, OR: 4.74; 95% CI: 1.82-12.30; $p = 0.019$) and no difference by gender was identified (Mantel–Haenszel estimate, OR: 1.11; 95% CI: 0.47-2.63; $p = 0.81$) (Table 2). The prevalence rate of naMCI-MD was 2.54% (95% CI: 1.83-3.52). It increased significantly with class of age (Mantel–Haenszel estimate, OR: 3.27; 95% CI: 1.78-6.01; $p < 0.05$) and no difference by gender was identified (Mantel–Haenszel estimate, OR:1.34; 95% CI: 0.75-2.41; $p = 0.32$) (Table 2). Finally, the prevalence rate of naMCI-SD was 2.76% (95% CI: 1.96-3.88). It increased significantly with class of age (Mantel–Haenszel estimate, OR: 2.08; 95% CI: 1.14-3.78; $p = 0.015$), while no difference by gender was identified (Mantel–Haenszel estimate, OR: 1.48; 95% CI: 0.81-2.70; $p = 0.20$) (Table 2).

### 3.3 | Relationships among biopsychosocial frailty, MCI, and its subtypes

In the present population-based study, 22 older individuals were identified as biopsychosocial frail with MCI (23.2%). Biopsychosocial frailty was associated with MCI (OR: 4.36; 95% CI: 2.60-7.29; Fisher's exact $p < 0.01$) (Table 3). Two older individuals were identified as biopsychosocial frail with aMCI-MD (2.11%). Biopsychosocial frailty was not associated with aMCI-MD (OR: 1.29; 95% CI: 0.30-5.46; Fisher's exact $p = 0.67$) (Table 3). Three older individuals were identified as biopsychosocial frail with aMCI-SD (3.16%). Biopsychosocial frailty was not

**TABLE 1** Sociodemographic and clinical characteristics [mean ± SD or median (25th–75th percentiles) or %] of older individuals with and without biopsychosocial frailty. Italian PRoject on the Epidemiology of Alzheimer's disease (IPREA)

| Variable | Whole cohort | With biopsychosocial frailty | Without biopsychosocial frailty | *p* value |
|---|---|---|---|---|
| | (n.1980) | (n.95) | (n.1885) | |
| Women (%) | 887 (44.8) | 65 (68.4) | 882 (43.6) | [a] < 0.05 |
| Age (years) | 72.3 ± 4.9 | 75.5 ± 4.7 | 72.1 ± 4.9 | * < 0.01 |
| Education (years) | 6.7 ± 4.2 | 4.9 ± 3.4 | 6.8 ± 4.2 | * < 0.01 |
| Pack-years | | | | |
| Former | 0 (0 – 17.5) | 0 (0 - 0) | 0 (0 - 18) | [b] > 0.0057 |
| Latter | 0 (0 - 0) | 0 (0 - 0) | 0 (0 - 0) | [b] > 0.9684 |
| Body mass index | 27.6 ± 4.4 | 29.1 ± 6.7 | 27.5 ± 4.2 | * < 0.01 |
| Mini-Mental State Examination | 27.4 ± 2.8 | 25.7 ± 4.1 | 27.5 ± 2.7 | * < 0.01 |
| Activities of daily living | 6.3 ± 1.0 | 8.4 ± 2.9 | 6.2 ± 0.7 | * < 0.01 |
| 30-item Geriatric Depression Scale | 7.3 ± 5.9 | 16.2 ± 6.3 | 6.8 ± 5.5 | * < 0.01 |
| Hypertension (%) | 1221 (61.7) | 68 (72.3) | 1153 (61.2) | [a] < 0.05 |
| Type-2 diabetes mellitus (%) | 293 (14.8) | 26 (27.7) | 267 (14.2) | [a] < 0.05 |
| Myocardial infarction (%) | 138 (7.0) | 7 (7.5) | 131 (7.0) | [a] 0.855 |
| Stroke (%) | 106 (5.4) | 23 (24.5) | 83 (4.4) | [a] < 0.05 |
| Congestive heart failure (%) | 51 (2.6) | 12 (12.6) | 39 (2.1) | [a] < 0.05 |
| Albumin (mg/dL) | 7.1 ± 9.1 | 6.2 ± 7.8 | 7.1 ± 9.2 | * 0.4014 |

*Student's t-test for independent samples.
[a]Pearson's $\chi 2$ test.
[b]Mann-Whitney U test.

associated with aMCI-SD (OR: 3.38; 95% CI: 0.98-11.71; Fisher's exact $p = 0.08$) (Table 3). Eleven older individuals were identified as biopsychosocial frail with naMCI-MD (11.6%). Biopsychosocial frailty was associated with naMCI-MD (OR: 6.92; 95% CI: 3.37-14.21; Fisher's exact $p < 0.01$) (Table 3). Six older individuals were identified as biopsychosocial frail with naMCI-SD (6.32%). Biopsychosocial frailty was associated with naMCI-SD (OR: 3.28; 95% CI 1.35-7.97; Fisher's exact $p = 0.02$) (Table 3).

## 4 | DISCUSSION

In the present large cohort of Italian older individuals from the population-based Italian IPREA, the prevalence rates of the biopsychosocial frailty phenotype and MCI were 6.8% and 8.2, respectively. Furthermore, this biopsychosocial frailty phenotype was associated with MCI and, in particular, could be associated with some of its subtypes, that is, naMCI-SD and naMCI-MD. No statistically significant associations between amnestic MCI single or multiple domain and biopsychosocial frailty were observed. The present findings suggested that a modifiable risk factor such as the biopsychosocial frailty phenotype may be associated with late-life cognitive decline, particularly MCI and naMCI.

In the IPREA, the prevalence of this biopsychosocial frailty phenotype was 6.8%, an estimate lower to those reported in population-based settings for physical frailty (12%)[31] and similar to those reported for cognitive frailty (1.0% to 4.4%)[5] and biopsychosocial frailty (5%) in another large population-based Italian study.[4] Given the multisystem and multidimensional nature of the biological changes underpinning the frail condition, among frailty phenotypes, the multiconcept biopsychosocial frailty may be of greater importance in predicting cognitive-related adverse outcomes in older age, however, at present, this model is not fully operationalized.[8] In fact, some hospital-[32,33] and population-based[34] findings suggested the biopsychosocial frailty phenotype as a predictor of adverse health-related outcomes, including functional disability, institutionalization, and mortality. For cognitive-related adverse outcomes, some longitudinal population-based studies investigated the risk of incident all-cause dementia[4,35–38] or AD.[4,39] In a very recent systematic review and meta-analysis on longitudinal studies investigating multiconcept frailty and late-life cognition, biopsychosocial frailty predicted a 41% higher risk of late-life cognitive decline or dementia and this phenotype also contributed to a 11% higher risk of AD.[40]

To the best of our knowledge, the present was the first study in which an association was found among biopsychosocial frailty, MCI, and its subtypes, particularly naMCI. In the past two decades, the construct of MCI has evolved to represent an intermediate stage of cognitive function between normal aging and dementia and may be useful in clinical practice since this condition may lead to a higher risk of progression to dementia.[28] In the present population-based

**TABLE 2** Prevalence of mild cognitive impairment (MCI) and its subtypes: Italian PRoject on the Epidemiology of Alzheimer's disease (IPREA)

| | | Age | | | |
|---|---|---|---|---|---|
| | | 65 – 74 years | | 75 – 84 years | |
| MCI | Gender | % (N) | 95% CI | % (N) | 95% CI |
| MCI | Men | 4.0% (4) | (2.7-5.6) | 10.0% (10) | (7.2-13.7) |
| | Women | 5.3% (5) | (3.8-7.4) | 13.6% (14) | (9.8- 18.7) |
| | Whole | 3.8% (9) | (2.6-5.5) | 9.7% (24) | (8.0-11.8) |
| Amnestic MCIsingle domain (aMCI-SD) | Men | 0.6% (1) | (0.2-1.5) | 1.8% (2) | (0.8-4.0) |
| | Women | 0.3% (0) | (0.1-1.3) | 2.9% (3) | (1.3-6.2) |
| | Whole | 0.3% (1) | (0.1-1.2) | 1.8% (5) | (1.0-2.9) |
| Amnestic MCI multiple domain (aMCI-MD) | Men | 1.2% (1) | (0.6-2.3) | 1.6% (2) | (0.8-3.0) |
| | Women | 1.3% (1) | (0.7-2.6) | 2.1% (2) | (0.9-4.5) |
| | Whole | 0.8% (2) | (0.4-1.8) | 1.8% (4) | (1.2-2.7) |
| Nonamnestic MCI single domain (naMCI-SD) | Men | 1.4% (1) | (0.7-2.5) | 3.1% (3) | (1.6-6.0) |
| | Women | 1.8% (2) | (1.0-3.3) | 4.8% (5) | (2.6-8.6) |
| | Whole | 1.3% (3) | (0.7-2.5) | 3.3% (8) | (2.2-4.7) |
| Nonamnestic MCI multiple domain (naMCI-MD) | Men | 0.8% (1) | (0.4-1.8) | 3.6% (4) | (2.1-6.1) |
| | Women | 1.8% (2) | (1.0-3.2) | 3.9% (4) | (2.1-7.2) |
| | Whole | 1.4% (3) | (0.7-2.6) | 2.9% (7) | (2.0-4.2) |

Abbreviations: CI, confidence interval; aMCI-MD = single domain amnestic MCI; aMCI-SD = multiple domain amnestic MCI; MCI, mild cognitive impairment; naMCI-MD = single domain nonamnestic MCI; naMCI-SD = multiple domain nonamnestic MCI.
*Note*: N = number of individuals according to the sampling weights by strata (400 individuals per 12 centers) and primary sampling units (PSU) (50 individuals per 8 PSU). The decimal values was rounded up or down to an integer value (the value rounded-up when the first decimal was 5 or greater, and rounded-down when the first decimal number was less than 5).

study, the prevalence rate of MCI was 8.2%, similar to the those found in population-based studies and ranging from 3% for subjects aged ≥60 years to 15% for people aged ≥75 years.[41] In a previous study on community-dwelling older subjects, higher biopsychosocial frailty increased dementia risk for people with either aMCI or naMCI, but the larger risk was in naMCI.[38] The present findings of a lack of association of the biopsychosocial frailty phenotype with aMCI-SD or aMCI-MD confirmed the greater adverse impact of this frailty phenotype on dementia risk for naMCI compared with aMCI.[38]

For the present CGA-based biopsychosocial frailty phenotype, examining data from the ILSA, we considered the physical frailty phenotype plus items mostly derived from the GDS-30 (concerning social participation and loneliness) and IADL (the use of the telephone, the ability to handle finances, and the ability to make transfers outside the home).[4] In this biopsychosocial frailty construct, the physical frailty domain impacted late-cognitive decline and this multifactorial association has several mediators or possible pathways implicated to explain the physical frailty-cognition links and hormonal and inflammatory processes, together with nutritional, vascular, neuropathological, and metabolic influences may be of major relevance.[5] The two GDS-30 items (3 and 10) identified by the best model evaluated the concept of loneliness and not of social participation.[4] In particular, the GDS-30 item 3 ("Do you feel that your life is empty?") can be compared with some aspects of psychosocial frailty emerging from the assessment scales used in other population-based studies,[42,43] characterized precisely by poor social contacts, inability and/or difficulty in social relationships and in transferring feelings, low emotional support, and loneliness. About the item 10 of GDS-30, ("Do you often feel helpless?"), the meaning of "feeling helpless" can be related to the magnitude of the instrumental and social support perceived by the older population so more linked to the concept of loneliness. Recently, two large systematic reviews and meta-analyses investigated the association of loneliness with MCI and dementia.[44,45] In particular, the first report, due to lack of sufficient data in longitudinal studies, did not explore the association between loneliness and risk of MCI through a meta-analysis, but limited evidence suggested a potential effect of loneliness on MCI.[44]The second meta-analysis conducted in cross-sectional and population-based studies from low- and middle-income countries showed that in older adults, overall, there was a significant association between loneliness and MCI (OR: 1.52; 95%CI: 1.12-2.07).[45] Loneliness may be associated with MCI through several mechanisms, including the triggering of neural responses that may directly influence the development of neurodegenerative conditions or the association with unhealthy behaviors including low levels of physical activity, substance abuse and poor nutrition, negatively affecting cognition either directly or via increased risk of cardiometabolic disease.[44] In the present study, the biopsychosocial frailty phenotype included also the physical frailty domain detected also with the presence of low levels of physical activity.

**TABLE 3** Relationships among biopsychosocial frailty (BF), mild cognitive impairment (MCI), and its subtypes: Italian PRoject on the Epidemiology of Alzheimer's disease (IPREA)

| MCI | | | aMCI-MD | | | aMCI-SD | | | naMCI-MD | | | naMCI-SD | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BF | Without MCI/ with MCI (*N* = 1836/144) | | | Without aMCI-MD/with aMCI-MD (*N* = 1947/33) | | | Without aMCI-SD/with aMCI-SD (*N* = 1959/21) | | | Without naMCI-MD/with naMCI-MD (*N* = 1934/46) | | | Without naMCI-SD/with naMCI-SD (*N* = 1936/44) | |
| | % | *P*<or= | BF | % | *P*<or= | BF | % | *P*<or= | BF | % | *P*<or= | BF | % | *P*<or= |
| Non-frail (*N* = 1885) | 93.5/6.5 | <0.01 | Non-frail (*N* = 1885) | 98.4/1.6 | = 0.67 | Non-frail (*N* = 1885) | 99.0/1.0 | = 0.08 | Non-frail (*N* = 1885) | 98.1/1.9 | <0.01 | Non-frail (*N* = 1885) | 98.0/2.0 | = 0.02 |
| Frail (*N* = 95) | 76.8/23.2 | | Frail (*N* = 95) | 97.9/2.1 | | Frail (*N* = 95) | 96.8/3.2 | | Frail (*N* = 95) | 88.4/11.6 | | Frail (*N* = 95) | 93.7/6.3 | |

The strengths of the present study were the population-based setting and the large number of older subjects included, notwithstanding a relatively small number of those with both biopsychosocial frailty and MCI. Furthermore, the fine distinctions of which MCI subtypes were and were not associated with biopsychosocial frailty were based on tiny numbers. However, given the population-based nature of the study, we had a relatively small sample size of older subjects with the biopsychosocial frailty phenotype and MCI and its subtypes, although our prevalence rates of these two entities (6.8% and 8.2%, respectively) were in line of those previously rated in subjects aged 65 years or more.[4,41] Therefore, biopsychosocial frailty could have a small effect on MCI, but in light of an increased number of people developing this condition in the near future and its progression towards overt dementia, it could have a great interest in terms of public health. However, given the cross-sectional nature of the study we cannot make any inference on the direction of the association because of reverse causality but can estimate association only in terms of prevalence. In fact, the biopsychosocial frailty construct identified subgroups of individuals deriving from the aggregation of physical and psychosocial functions that were cross-sectionally observed. Moreover, in the IPREA, among factors that are potential risk factors for dementia and might be associated with some frailty components, thereby acting as potential confounders, we did not have information on the apolipoprotein E (*APOE*) ε4 allele status. However, the increased risk of both MCI and dementia associated with frailty was found to be independent of the presence of the *APOE* ε4 allele.[46]

In conclusion, different frailty phenotypes have been associated with late-life cognitive impairment/decline, incident dementia, AD, MCI, VaD, non-AD dementias, and AD pathology.[5] However, the vulnerability of older adults at risk of developing dementia is not completely captured by the biological perspective of frailty and the biopsychosocial model may add important value in both assessment and target of intervention in older age. Considering the present findings and those of other epidemiological studies,[4,35–40] it may be prudent to implement public health policy and intervention to reduce the impact of the biopsychosocial frailty phenotype and to aid in the prevention of MCI and ultimately dementia. While secondary preventive strategies for cognitive impairment and the physical frailty domain of the biopsychosocial frailty phenotype should be suggested, with an individualized multidomain interventions targeting physical and nutritional domains that may delay MCI onset and the progression to overt dementia,[47] some primary intervention strategies have been identified to reduce the impact of the psychosocial domain of the biopsychosocial frailty phenotype that included the improvement of social skills, the enhancement of social support, the increase of opportunities for social contact, and addressing maladaptive social cognition.[48] In the next future, prospective population-based studies evaluating the association between the biopsychosocial frailty phenotype and incident MCI and its progression to dementia are needed, addressing also potential bias and confounding sources.

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## CONFLICT OF INTEREST

The authors declare no competing interests.

## INFORMED CONSENT

For this type of study, formal consent is not required.

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## APPENDIX

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