



Applied nutritional investigation

Undernutrition impacts on cognitive performance trajectories in older adults: The collaborative PROMED-COG pooled cohorts study

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ABSTRACT

Objectives: The aim of this retrospective study was to investigate the association between undernutrition and the trajectories of neurocognitive aging.

Methods: We used harmonized data from two population-based longitudinal studies: the Progetto Veneto Anziani and the Italian Longitudinal Study on Aging. Both studies included a baseline and two follow-up evaluations over 9 y. Undernutrition was defined according to the Global Leadership Initiative on Malnutrition criteria, and cognitive function was assessed using the Mini-Mental State Examination.

Results: The analytical sample comprised 3852 individuals (46% female) aged 65 to 96 y. During follow-up, growth mixture modeling identified three Mini-Mental State Examination score trajectories. Trajectory 1 (4.8% of participants) was characterized by a steep decline, trajectory 2 (22.1% of participants) by a gradual decrease, and trajectory 3 (73.1% of participants) by high scores that remained nearly stable throughout the follow-up period. Overall, 540 participants (14.1%) had undernutrition, with a prevalence significantly higher in trajectory 1 (26.9%) than in trajectory 2 (17.3%) or trajectory 3 (12.2%). Baseline undernutrition was associated with a higher probability of belonging to the rapidly decreasing trajectory 1 (odds ratio, 1.71, 95% confidence interval, 1.06–2.77, reference, trajectory 3), a finding driven mainly by the phenotypic Global Leadership Initiative on Malnutrition criteria.

Conclusions: Undernutrition is associated with steeper cognitive decline in older adults, particularly when phenotypic signs are present. However, given the potential bidirectional relationship between cognitive status and undernutrition, reverse causation cannot be ruled out entirely. Nevertheless, our findings underscore the importance of assessing nutritional status in advanced age, as it represents a modifiable factor that may delay or prevent cognitive decline.

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Introduction

Aging is associated with reduced adaptive capacity, leading to metabolic, physiological, and functional impairments as well as an increased likelihood of multimorbidity, frailty, and disability [1]. This time-related process may also involve cognitive decline,

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which accelerates with advancing age [2]. However, significant differences are observed in the trajectories of neurocognitive aging, ranging from the maintenance of high cognitive and functional capacities to the development of neurocognitive disorders [3,4]. Most older adults, however, fall into an intermediate condition of “normal aging,” characterized by a modest decline in cognitive abilities, with varying impacts on functional status [2].

Although genetic factors contribute to aging trajectories [3], increasing evidence underscores the importance of environmental and behavioral influences, including lifestyle. The 2020 Lancet Commission on dementia outlined 12 modifiable risk factors from early to late life that, collectively, could prevent 40% of cases [5]. This shift toward the idea that cognitive decline is not inevitably tied to intrinsic aging determinants but is instead influenced by modifiable factors offers a window of opportunity.

Among the proposed measures, maintaining adequate nutritional status has been recognized as an important factor [6,7]. Indeed, undernutrition, a condition characterized by reduced nutrient uptake or intake [8], is common in older adults [1] and is associated with adverse outcomes [9,10]. Notably, some studies have observed that undernutrition is associated with a higher risk of dementia and could intensify cognitive and functional decline in older adults with dementia [11].

In this regard, although undernutrition may precede the diagnosis of cognitive decline by approximately 10 y, overt symptoms of dementia typically appear considerably later during neurodegenerative processes [12], leaving the question open as to which condition truly comes first. However, the literature provides substantial evidence for the possible role of lifelong nutrition in brain integrity, brain volume, and clinical measures of cognitive health [13], and undernutrition has been associated with accelerated atrophy in areas vulnerable to Alzheimer's disease [14]. Nevertheless, little is known about how exposure to undernutrition longitudinally affects the rate of cognitive decline. A previous study found that older adults identified as being at global risk of malnutrition were more likely to experience cognitive decline or develop incident mild cognitive impairment or dementia over a 3- to 5-y follow-up period [15]. Moreover, poor nutritional status was associated with a reduced lifespan and an accelerated progression to severe dementia in cognitively impaired older adults [11].

Recently, the Global Leadership Initiative on Malnutrition (GLIM) has proposed new diagnostic criteria for undernutrition, incorporating both phenotypic and etiologic factors [16]. This approach is grounded in a consensus on widely used evidence-based criteria [9,16]. To the best of our knowledge, no studies have examined the impact of undernutrition on cognitive function using the GLIM guidelines. Thus, the aim of this study was to investigate the association between undernutrition, defined according to the latest GLIM recommendations, and trajectories of neurocognitive aging and to determine whether phenotypic or etiologic criteria are similarly associated with cognitive decline.

Materials and methods

Study population

This study is part of the protein-enriched Mediterranean diet to combat undernutrition and promote healthy neurocognitive aging in older adults (PROMED-COG) initiative funded by the European Horizon 2020 Joint Programming Initiative “A Healthy Diet for a Healthy Life” (JPI HDHL) and the ERA-NET Cofund ERA-HDHL [17]. One activity of PROMED-COG was to explore the potential impact of undernutrition on neurocognitive aging in older adults using existing epidemiologic data. For this work, we considered data from two population-based studies, described briefly as follows:

- Progetto Veneto Anziani (Pro.V.A.) is a prospective study that included an age- and sex-stratified random sample of 3099 individuals aged ≥ 65 y living in two cities in Northern Italy [18]. Participants underwent a baseline evaluation in 1995 to 1997, with follow-up assessments in 1999 to 2000 and 2002 to 2004. Evaluations were conducted by trained nurses and physicians in the hospital or at home, collecting data on sociodemographic characteristics, lifestyle factors, risky behaviors, cognitive and physical performance, functional status, laboratory parameters, and chronic diseases through personal interviews, medical record review, administration of validated scales and tests, and physical examinations.
- The Italian Longitudinal Study on Aging (ILSA) is a prospective study that included 5632 individuals aged 65 to 84 y selected randomly from the demographic lists of the registry offices of eight municipalities in Northern, Central, and Southern Italy. Details of the study can be found in previous publication [19]. The baseline evaluation was conducted in 1992 to 1993, and follow-up assessments were conducted in 1995 to 1996 and 2000 to 2001. Participants' evaluations included a face-to-face interview covering sociodemographic information, self-reported chronic diseases, risky behaviors, laboratory tests, physical performance, and diagnostic examinations. Furthermore, individuals identified as having suspected diabetes mellitus, cardiovascular disease (CVD), or neurologic disease during the initial examinations underwent a more thorough clinical assessment by a specialist to confirm the diagnosis [20].

The protocols of the ILSA and Pro.V.A. complied with the principles of the Declaration of Helsinki and were approved by local ethics committees (for the ILSA, by the institutional review board of the eight participating municipalities; for the Pro.V.A., by the ethics committees of the University of Padova and local health units No. 15 and No. 18 of the Veneto region). All participants provided their written informed consent to participate in the study.

Data collection

The two aforementioned population-based studies underwent retrospective data harmonization in accordance with published guidelines [21]. In particular, seven main domains were considered for harmonization: 1) general information; 2) sociodemographic data, including sex, age, educational level, occupation performed for most of the individual's working life (categorized as blue or white collar [22]), civil status, and socioeconomic status (defined as both education and occupation performed for most of the individual's working life [23]); 3) anthropometric variables, including weight at baseline and follow-up visits, self-reported weight at 50 y, weight loss in the last year, and body mass index (BMI) as well as waist, hip, and midarm circumference [8]; 4) variables related to GLIM etiologic criteria, including bowel or stomach disease, liver or gallbladder disease, chronic bronchitis or emphysema or asthma, cancer, bone or joint disease, heart failure, and laboratory parameters linked to inflammatory or nutritional status (i.e., white blood cell count, neutrophils, monocytes, lymphocytes, eosinophils, basophils, fibrinogen, and serum albumin); 5) risky behaviors (smoking and drinking habits); 6) cardio-metabolic risk factors (hypertension, hyperlipidemia, and limited mobility) and chronic conditions, including diabetes, CVD (angina, ischemic heart disease, arrhythmia, peripheral artery disease, and stroke), and depressive symptoms; and 7) cognitive health, assessed at baseline and follow-up visits using the Mini-Mental State Examination (MMSE) [24], and diagnosis of dementia.

Nutritional status

Undernutrition was operationalized using the GLIM criteria, requiring the presence of at least one phenotypic criterion and at least one etiologic criterion (Supplementary Table 1) [16]. Phenotypic criteria included low BMI (< 20 kg/m² if < 70 y or < 22 kg/m² if ≥ 70 y), as recommended by the GLIM consensus [16]; reduced muscle mass based on midarm circumference using validated age- and sex-specific references [25]; and weight loss > 5 kg in the previous year. The etiologic criteria included conditions related to low food assimilation (e.g., bowel or stomach disease, liver or gallbladder disease) or inflammatory status (e.g., neoplasms, congestive heart failure, chronic obstructive pulmonary disease, or bone and joint disease) as well as biochemical markers of inflammation and nutritional status (e.g., high fibrinogen or elevated white blood cell count above the age- and sex-specific median values or low albumin levels below the age- and sex-specific median values to account for physiological variation across demographic groups and to ensure comparability across pooled populations with potential differences in laboratory assays).

Cognitive function

Cognitive performance was evaluated using the MMSE (unadjusted scores) at baseline and at two follow-up visits, yielding up to three MMSE measurements per participant, with an overall follow-up period of approximately 9 y. Participants also underwent a clinical examination and a review of medical records to assess dementia at baseline and throughout the study period. For the Pro.V.A., hospital discharge records (*International Classification of Diseases, Ninth Revision* codes) and causes of death (*International Classification of Diseases, Ninth Revision* codes)

related to dementia were considered. For the ILSA, in addition to the clinical assessment based on the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* criteria for the dementia syndrome [26] and the NINCDS-ADRDA criteria for possible and probable Alzheimer's disease [27], *International Statistical Classification of Diseases, Tenth Revision* codes for vascular dementia and other dementing diseases were identified from hospital records and cause-of-death registers [20].

Statistical analysis

Quantitative variables were expressed as mean $\pm$ standard deviation or as median and interquartile range, whereas categorical variables were reported as count and percentage. MMSE score trajectories over the follow-up period were assessed using group-based trajectory modeling and SAS Proc Traj [28], which allows for the identification of distinct trajectories within a population when grouping variables that are not known a priori [29]. By maximizing the log-likelihood function, an average growth curve, with its intercept, slope, and growth parameter variance, was identified for each group [30], and the probability of belonging to each identified group was estimated for participants based on the observed data, with assignment to the group with the higher posterior probability. Several models were defined, ranging from 1- to 5-group models, with polynomials of varying degrees within each group. Model selection was based on the following criteria:

- Models were compared using the Bayesian Information Criterion (BIC), and $2\Delta\text{BIC}$ (twice the difference in BIC between less and more complex models) >10 was considered an indicator of substantial improvement in fit.
- Trajectory groups needed to include at least 5% of the sample to ensure clinical relevance and adequate statistical power for subsequent analyses.
- The average posterior probability of membership (entropy) should be >0.7 , indicating adequate internal reliability.

Differences between identified MMSE score trajectory groups were evaluated using generalized linear models after testing for homoscedasticity (Levene's test) as well as Wilcoxon rank-sum, χ^2 , or Fisher's exact tests, as appropriate. Bonferroni adjustments were applied to account for multiple comparisons, as appropriate. Multinomial logistic regression models were then used to assess the association between undernutrition and MMSE trajectory groups, adjusting for sex, age, education, previous occupation, marital status, smoking habits, alcohol consumption, diabetes, hyperlipidemia, CVD, depression, and limited mobility. Further models were defined, adjusting for dementia. The strength of the associations was expressed using odds ratio (OR) and 95% confidence interval (CI). Sensitivity analyses were conducted, separately considering the presence of at least one

phenotypic or one etiologic GLIM criterion, using commonly adopted clinical cut-offs to enhance clinical interpretability of albumin (<35 g/dL), fibrinogen (>400 mg/dL), and white blood cell count ($>11,000$) to assess robustness of the findings, and multiple imputations of missing data based on the fully conditional specification method (10 imputed data sets created and then combined using PROC MIANALYZE) were also evaluated. To reduce the likelihood of malnutrition being a marker of preexisting cognitive impairment rather than a determinant, we conducted additional sensitivity analyses, excluding participants with dementia at baseline and also focusing on those with preserved cognitive function (MMSE score ≥ 24).

Two-tailed P values less than 0.05 were considered statistically significant. The analyses were performed using the statistical package SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

From a total of 8731 individuals derived from the pooling of the two original data sets, we excluded those living in institutions or nursing homes ($n = 175$), those who did not participate in the baseline survey or were ineligible ($n = 1089$), and those with missing information required for the analyses ($n = 3615$). The final analytical sample included 3852 individuals (46% female) aged 65 to 96 y. Participants included in the analyses were significantly younger, more likely to be female, and less educated and had a lower prevalence of diabetes, CVD, depressive symptoms, and walking disability compared with those excluded because of missing values (Supplementary Table 2).

Based on the comparison of models with one to five trajectory groups (Supplementary Table 3), a three-group solution was selected as optimal, balancing BIC improvement, minimum group size (all $\geq 5\%$ of the sample), and acceptable classification quality. Three trajectories for MMSE scores were identified over the follow-up period, considering group-based trajectory modeling (Fig. 1):

- Trajectory 1 ($n = 186$ [4.8%], 95% CI, 4.2–5.6) showed rapidly declining MMSE scores, with a mean baseline score of 18.1,

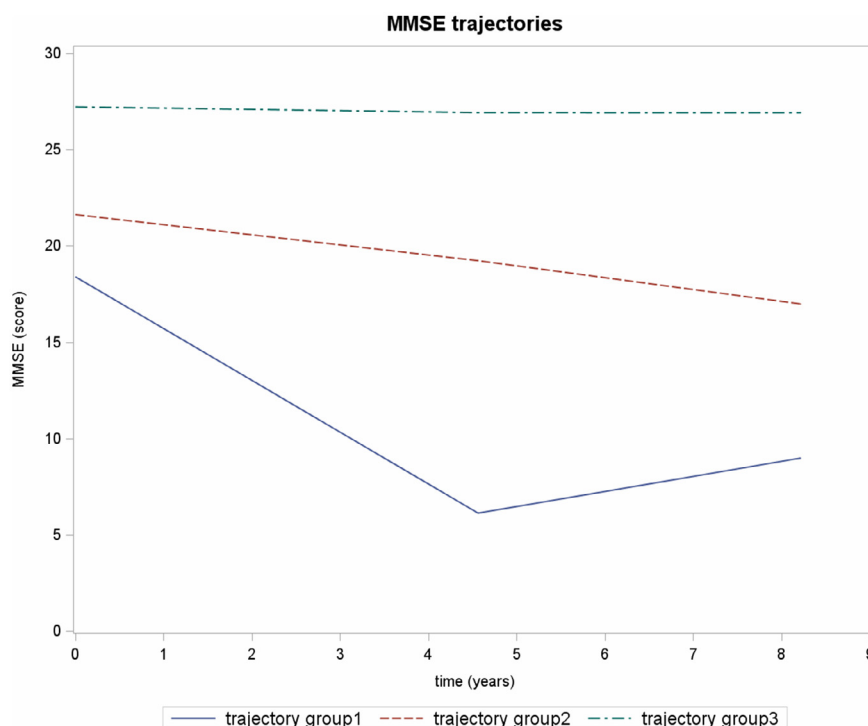


Fig. 1. Trajectory pattern of MMSE scores. MMSE, Mini-Mental State Examination.

decreasing to 5.6 at the first follow-up, and then increasing to 8.4 at the last follow-up. The apparent improvement in MMSE scores is unlikely to reflect actual cognitive recovery and is more plausibly explained by selective survival.

- Trajectory 2 ($n = 851$ [22.1%], 95% CI, 20.8–23.4) showed gradually decreasing scores, with a mean baseline MMSE score of 21.5 and mean follow-up scores of 19 and 16.6.
- Trajectory 3 ($n = 2815$ [73.1%], 95% CI, 71.7–74.5) showed consistently high scores throughout the follow-up period, with a baseline mean MMSE score of 27.2 and follow-up mean scores of 26.9 at both follow-up visits.

Individuals in trajectory 1 were older (81.3 ± 5.9 y) and more likely to be female and to have hypertension, diabetes, CVD, and depressive symptoms at baseline as well as lower mean MMSE scores than those in trajectories 2 and 3 (Table 1). By contrast, participants in trajectory 3 were younger (71.8 ± 5.0 y) and more likely to be male; they had higher educational levels and

socioeconomic status and a lower prevalence of chronic diseases, except for hyperlipidemia, compared with trajectory 1.

Among the anthropometric parameters, we found significant differences in midupper arm circumference and body weight, which were higher in trajectory 3 participants, and in hip circumference and weight loss over the past year, which were lower in trajectory 3 participants than in trajectory 1 participants (Table 2). Regarding the GLIM etiologic criteria variables, gastrointestinal and hepatobiliary diseases were more frequent among trajectory 3 participants, whereas the opposite was true for bone diseases and congestive heart failure. Overall, 540 participants (14.1%) were undernourished, and their frequency decreased significantly from trajectory 1 ($n = 50$ [26.9%]) to trajectory 2 ($n = 147$ [17.3%]) and trajectory 3 ($n = 343$ [12.2%]).

The results of the multinomial logistic regression models evaluating the association between undernutrition and MMSE scores are shown in Table 3. After adjusting for potential confounders and considering trajectory 3 (consistently high scores) as the reference,

Table 1
Characteristics of study participants according to identified MMSE trajectories

Variable	All ($n = 3852$)	Trajectory 1 ($n = 186$)	Trajectory 2 ($n = 851$)	Trajectory 3 ($n = 2815$)	P value
Age (mean $\pm$ SD [y])	73.7 $\pm$ 6.2	81.3 $\pm$ 5.9	78.3 $\pm$ 6.2	71.8 $\pm$ 5.0	< 0.001 ^{§,¶}
Sex (No. [%] [female])	1758 (45.6)	131 (70.4)	557 (65.5)	1406 (50.0)	< 0.001 [¶]
Education (No. [%])					< 0.001 ^{§,¶}
Primary school or less	3070 (79.8)	175 (95.1)	827 (97.5)	2068 (73.5)	
Middle school	373 (9.7)	5 (2.7)	15 (1.8)	353 (12.5)	
High school	241 (6.3)	2 (1.1)	6 (0.7)	233 (8.3)	
University or higher	162 (4.2)	2 (1.1)	0 (0.0)	160 (5.7)	
Work done most of the time (No. [%])					< 0.001 [¶]
Housewife	557 (14.7)	30 (16.5)	145 (17.2)	382 (13.8)	
Blue collar	2148 (56.7)	119 (65.8)	569 (67.5)	1460 (52.8)	
White collar	1087 (28.7)	32 (17.7)	129 (15.3)	926 (33.4)	
Marital status (No. [%])					< 0.001 [¶]
Single or never married	246 (6.4)	16 (8.6)	55 (6.5)	175 (6.2)	
Married or cohabiting	1869 (60.1)	64 (34.4)	380 (44.7)	1869 (66.4)	
Separated or divorced	22 (0.5)	0 (0.0)	2 (0.2)	20 (0.7)	
Widowed	1269 (33.0)	106 (57.0)	413 (48.6)	750 (26.7)	
SES * (No. [%])					< 0.001 [¶]
1 low	2711 (70.4)	154 (82.8)	721 (84.8)	1836 (65.2)	
2 medium	790 (20.5)	28 (15.0)	123 (14.5)	639 (22.7)	
3 high	340 (9.1)	4 (2.2)	6 (0.7)	340 (12.1)	
Lifestyle factors					
Smoking status (No. [%])					< 0.001 [¶]
Current smoker	443 (11.5)	8 (4.3)	60 (7.1)	375 (13.3)	
Former smoker	1247 (32.4)	42 (22.6)	189 (22.2)	1016 (36.1)	
Never smoker	2159 (56.1)	136 (73.1)	602 (70.7)	1421 (50.5)	
Alcohol consumption (No. [%])					< 0.001 ^{§,¶}
Heavy consumer [†]	668 (17.4)	17 (9.1)	122 (14.4)	527 (18.7)	
Light consumer [‡]	1085 (28.2)	32 (17.2)	217 (25.5)	1451 (51.6)	
Non-consumer	2098 (54.5)	137 (73.7)	510 (60.1)	836 (29.7)	
Cardiometabolic and other health status factors					
Hypertension (No. [%])	2624 (68.2)	142 (76.3)	614 (72.2)	1868 (66.4)	< 0.001 [¶]
Diabetes (No. [%])	491 (12.8)	29 (15.6)	130 (15.3)	332 (11.8)	0.015
Hyperlipidemia (No. [%])	1406 (38.0)	24 (17.3)	264 (32.6)	1118 (40.7)	< 0.001
CVD (No. [%])	1101 (33.0)	70 (42.7)	255 (35.4)	776 (31.7)	0.005 ^{§,¶}
Depressive symptoms (No. [%])	1172 (31.8)	64 (45.4)	355 (43.8)	753 (27.5)	< 0.001 [¶]
Walking ability (No. [%])	3706 (97.9)	167 (90.8)	788 (94.7)	2751 (99.4)	< 0.001 [¶]
Physical activity ≥ 4 h/wk (No. [%])	548 (25.9)	22 (14.9)	89 (15.9)	437 (31.1)	< 0.001 [¶]
Weight at age 50 (mean $\pm$ SD [kg])	66.7 $\pm$ 11.6	63.7 $\pm$ 11.4	64.5 $\pm$ 11.4	67.5 $\pm$ 11.5	< 0.001 [¶]
MMSE at baseline (mean $\pm$ SD)	25.5 $\pm$ 4.0	18.1 $\pm$ 6.0	21.5 $\pm$ 3.3	27.2 $\pm$ 2.3	< 0.001 ^{§,¶}
Dementia at baseline (No. [%])	33 (0.9)	10 (5.4)	16 (1.9)	7 (0.3)	< 0.001 ^{§,¶}

CVD, cardiovascular disease; MMSE, Mini-Mental State Examination; SD, standard deviation; SES, socioeconomic status

*Composite measure defined considering education (primary or middle school = score 1, high school or university or more = score 2) and work done most of the time (blue collar or housewife = score 1, white collar = score 2), with total score 1 or 2 corresponding to SES = 1 (low), total score 3 corresponding to SES = 2 (medium), and total score 4 corresponding to SES = 3 (high)

[†] ≥ 7 AU/wk women, ≥ 14 AU/wk men.

[‡] < 7 AU/wk women, < 14 AU/wk men.

[§] $P < 0.05$ post hoc trajectory 1 vs 2.

[¶] $P < 0.05$ post hoc trajectory 1 vs 3.

[¶] $P < 0.05$ post hoc trajectory 2 vs 3.

Table 2

Factors related to GLIM criteria according to identified MMSE trajectories

Variable	All (n = 3852)	Trajectory 1 (n = 186)	Trajectory 2 (n = 851)	Trajectory 3 (n = 2815)	P value
Factors related to GLIM phenotypic criteria					
BMI (mean $\pm$ SD [kg/m ²])	27.5 $\pm$ 4.5	27.3 $\pm$ 4.9	27.7 $\pm$ 4.8	27.4 $\pm$ 4.4	0.412
BMI (No. [%] [kg/m ²])					0.104
<18.5	39 (1.0)	4 (2.1)	9 (1.1)	26 (0.9)	
18.5–24.9	1080 (28.3)	59 (32.1)	237 (28.2)	784 (28.1)	
25–29.9	1762 (46.2)	71 (38.6)	370 (44.0)	1321 (47.3)	
≥ 30	937 (24.5)	50 (27.2)	225 (26.7)	662 (23.7)	
Low BMI according to GLIM criteria* (No. [%])	249 (6.5)	21 (11.4)	78 (9.3)	150 (5.4)	< 0.001 ^{1,4,5}
Waist circumference (mean $\pm$ SD [cm])	96.7 $\pm$ 11.6	96.0 $\pm$ 11.7	96.3 $\pm$ 11.7	96.9 $\pm$ 11.6	0.315
Midupper arm circumference (mean $\pm$ SD [cm])	30.3 $\pm$ 4.7	29.2 $\pm$ 3.5	30.1 $\pm$ 6.1	30.6 $\pm$ 4.1	< 0.001 [‡]
Hip circumference (mean $\pm$ SD [cm])	101.4 $\pm$ 15.3	104.4 $\pm$ 54.9	100.4 $\pm$ 9.8	101.5 $\pm$ 9.6	0.013 ^{1,‡}
Weight (mean $\pm$ SD [kg])	69.5 $\pm$ 13.0	64.7 $\pm$ 12.2	66.5 $\pm$ 13.4	70.7 $\pm$ 12.8	< 0.001 ^{1,4,5}
Weight loss in the last year >5 kg (No. [%])	328 (8.7)	30 (16.6)	82 (9.9)	216 (7.8)	< 0.001 [‡]
Factors related to GLIM etiologic criteria					
Self-reported bowel or stomach disease (No. [%])	1341 (34.9)	59 (31.9)	264 (31.2)	1018 (36.3)	0.016
Self-reported liver or gallbladder disease (No. [%])	986 (25.9)	37 (19.9)	196 (23.3)	753 (27.1)	0.014
Self-reported chronic bronchitis (No. [%])	618 (16.2)	27 (14.8)	127 (15.2)	464 (16.7)	0.516
Self-reported cancer (No. [%])	207 (5.4)	10 (5.4)	52 (6.1)	145 (5.2)	0.572
Self-reported bone disease (No. [%])	248 (62.7)	136 (73.5)	601 (70.9)	1671 (59.6)	< 0.001 ^{1,5}
Congestive heart failure (No. [%])	220 (5.7)	25 (13.4)	89 (10.5)	106 (3.8)	< 0.001 ^{1,5}
Albumin (mean $\pm$ SD [g])	57.8 $\pm$ 16.3	57.2 $\pm$ 6.8	58.4 $\pm$ 6.4	57.6 $\pm$ 18.7	0.396
Fibrinogen (mean $\pm$ SD [mg/dL])	340.9 $\pm$ 99.9	358.5 $\pm$ 91.3	342.3 $\pm$ 79.4	339.3 $\pm$ 105.8	0.046
White blood cell count (mean $\pm$ SD [$\times 1000/\text{mm}^3$])	6.0 $\pm$ 2.2	6.6 $\pm$ 4.2	6.1 $\pm$ 2.2	5.9 $\pm$ 2.0	< 0.001 ^{1,4,5}
Undernutrition according to GLIM (No. [%])	540 (14.1)	50 (26.9)	147 (17.3)	343 (12.2)	< 0.001 ^{1,5}

BMI, body mass index; GLIM, Global Leadership Initiative on Malnutrition; MMSE, Mini-Mental State Examination; SD, standard deviation

* <20 kg/m² if age <70 y, <22 kg/m² if age ≥ 70 y.¹ P < 0.05 post hoc trajectory 1 vs 2.[‡] P < 0.05 post hoc trajectory 1 vs 3.⁵ P < 0.05 post hoc trajectory 2 vs 3.

we found that undernutrition at baseline was significantly associated with the rapidly declining trajectory 1 (OR, 1.71, 95% CI, 1.10–2.88, $P = 0.018$) but not with trajectory 2 (OR, 1.14, 95% CI, 0.86–1.51, $P = 0.355$). Results were confirmed when models were additionally adjusted for dementia (trajectory 1 versus 3, OR, 1.74, 95% CI, 1.08–2.83, $P = 0.024$; trajectory 2 versus 3, OR, 1.13, 95% CI, 0.85–1.50, $P = 0.412$) and when considering only participants with baseline MMSE score ≥ 24 (trajectory 1 versus 3, OR, 2.55, 95% CI, 1.01–6.42, $P = 0.047$; trajectory 2 versus 3, OR, 0.81, 95% CI, 0.50–1.32, $P = 0.401$). No significant differences were observed when males and females were considered separately (males, OR, 1.83, 95% CI, 0.77–4.53 for trajectory 1 versus 3, OR, 1.31, 95% CI, 0.84–2.04 for trajectory 2 versus 3; females, OR, 1.78, 95% CI, 0.99–3.22 for trajectory 1 versus 3, OR, 1.03, 95% CI, 0.71–1.49 for trajectory 2 versus 3). This association was also confirmed for the phenotypic GLIM criteria (OR, 1.71, 95% CI, 1.06–2.77, $P = 0.028$). Results were substantially unchanged in sensitivity analyses using clinical biomarker cutoffs (Supplementary Table 4). The association was confirmed in models with multiple imputations for missing data, which included participants initially excluded because of incomplete data (trajectory 1 versus 3, OR, 1.71, 95% CI, 1.13–2.59, $P = 0.011$; trajectory 2 versus 3, OR, 1.20, 95% CI, 0.86–1.66, $P = 0.276$), thus supporting the robustness of our findings. In

sensitivity analyses excluding participants with dementia at baseline, the association between undernutrition and MMSE trajectories was also confirmed (trajectory 1 versus 3, OR, 1.82, 95% CI, 1.12–2.97; trajectory 2 versus 3, OR, 1.17, 95% CI, 0.88–1.56).

Discussion

In this study, we investigated the association between undernutrition, as defined by GLIM criteria, and trajectories of neurocognitive aging in a retrospective pooled cohort. The main findings indicate that older adults exposed to undernutrition had poorer cognitive function and were more likely to experience rapid cognitive decline over time than well-nourished individuals. This relationship was driven by the presence of phenotypic criteria of undernutrition; namely, low body weight, reduced muscle mass, or weight loss. The main findings of the present work are consistent with previous studies suggesting that poor nutritional status is a significant predictor of cognitive decline and dementia in healthy adults as well as worse dementia prognosis, characterized by faster decline and mortality [15,11].

In our cohort, the growth mixture modeling allowed us to identify three trajectories of neurocognitive aging. Trajectory 1 was characterized by poorer cognitive function at baseline, consistent

Table 3

Association between undernutrition and MMSE trajectories

Variable	MMSE trajectory pattern 1 vs 3			MMSE trajectory pattern 2 vs 3		
	OR	95% CI	P value	OR	95% CI	P value
Undernutrition at baseline	1.78	1.10–2.88	0.018	1.14	0.86–1.51	0.355
At least one phenotypic criterion	1.71	1.06–2.77	0.028	1.13	0.85–1.49	0.403
At least one etiologic criterion	2.91	0.38–22.0	0.302	0.96	0.54–1.71	0.894

CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio

Model adjusted for sex, age, education, work done, marital status, smoking status, alcohol consumption, diabetes, hyperlipidemia, cardiovascular disease, depression, and limited mobility

with mild to moderate cognitive deficits, followed by a steep decline to severe cognitive impairment. An apparent improvement trend was observed in only this group at the final follow-up. This pattern is unlikely to reflect an actual improvement in cognitive function and is more plausibly explained by selective survival and differential attrition, in which individuals with more severe cognitive impairment are less likely to be observed in later follow-up assessments [31,32]. Trajectory 2 exhibited a higher baseline score and a more gradual decline, with MMSE scores indicating a slight cognitive decline that was less pronounced than in the first trajectory. Trajectory 3 comprised individuals who demonstrated well-preserved and stable cognitive function over time. These groups are representative of the spectrum of aging and the various patterns documented in the literature, from individuals who successfully age (the “super-normals” [3]) to those who experience normal aging, exhibiting a modest and variable decline in cognitive abilities, and those who develop steeper cognitive deterioration leading to dementia.

The overall prevalence of undernutrition in our cohort was 14.1%, in line with previous studies and reviews of the older population [1,33,34]. This prevalence varied significantly across the three trajectory groups, reaching its highest value in the group with poorer cognitive function and decreasing in the group with higher cognitive performance over the study period, consistent with the current literature [11,35]. This association remained significant after controlling for potential confounders, including sociodemographics, risk behaviors, chronic conditions, and limited mobility. By contrast, no substantial results were observed for trajectory 2 (exhibiting gradual cognitive decline), although the prevalence of undernutrition at baseline in this group was significantly higher than in trajectory 3, in which cognitive function remained stable over time.

According to the GLIM criteria, individuals in trajectory 1 had lower midupper arm circumference and lower baseline weight, suggesting decreased body and muscle mass. Another anthropometric factor distinguishing the trajectory with steeper cognitive decline was weight at age 50. Similarly, previous longitudinal studies have found that weight loss can precede dementia onset by as much as 11 to 20 y [36,37]. Regarding the etiologic criteria, individuals in trajectory 1 exhibited a higher prevalence of bone diseases and congestive heart failure, conditions characterized by chronic inflammation that may affect nutritional and cognitive status [38,39].

The GLIM criteria emphasize the importance of considering both etiologic and phenotypic criteria in diagnosing malnutrition [16]. Analyzing the differential association of these criteria with trajectories of neurocognitive aging in our data revealed that phenotypic criteria played a predominant role. However, it is important to acknowledge that these phenotypic criteria—namely, weight loss and reduced BMI and muscle mass—are not exclusively nutritional markers but may also capture the presence of broader geriatric syndromes, such as frailty and sarcopenia, which are known to be associated with steeper cognitive decline in advanced age [40]. This result also aligns with the recommended approach to using GLIM criteria [16]. Although diagnosing malnutrition requires a combination of at least one phenotypic and one etiologic criterion, it is recommended to use phenotypic criteria cut points to provide severity grading. Overall, these data reinforce the importance of closely monitoring any signs of weight loss and alterations in body mass in older adults.

Our findings do not allow us to definitively determine the direction of the causal relationship between undernutrition and cognitive decline. Given the observational nature of the study, it is not possible to make definite causal inferences, and different

interpretations of the observed associations may be plausible. Indeed, participants in the rapidly declining trajectory group (trajectory 1), which had the highest prevalence of undernutrition, showed substantially lower MMSE scores and a higher prevalence of dementia at baseline. This imbalance could be due at least in part to reverse causation; that is, preexisting cognitive impairment may contribute to subsequent undernutrition through mechanisms such as apathy, executive dysfunction, difficulty swallowing, or reduced ability to obtain, prepare, and consume food. In turn, epidemiologic and clinical evidence indicates that undernutrition may accelerate or exacerbate cognitive decline, suggesting a reciprocal, self-reinforcing relationship between these conditions. Therefore, rather than a simple unidirectional pathway, the relationship between undernutrition and cognitive decline may reflect complex bidirectional interactions evolving over time. Notably, the observation that individuals in this group had lower weight at age 50 supports the hypothesis that long-term nutritional factors may influence cognitive trajectories in later life and that weight loss or its underlying processes could contribute to the progression of cognitive impairment [37]. Additional sensitivity analyses excluding participants with dementia at baseline confirmed the main results. Despite these considerations, our results suggest that undernutrition may play a significant and potentially independent role in the longitudinal trajectory of cognitive function in aging. Individuals who are undernourished are more likely to have reduced caloric intake and micronutrient deficiencies, which may influence inflammatory processes and oxidative stress mechanisms, both of which are known to be key contributors to neurodegeneration [41,42]. Although this study did not specifically focus on single-nutrient deficits, it is plausible that these factors play a significant role in the observed outcomes. Overall, these findings have significant implications for daily clinical practice. Nutritional status is an easily assessable factor that can be managed through lifelong preventive measures and is included among modifiable lifestyle factors. Despite growing awareness of its importance and clinical recommendations to routinely screen patients for undernutrition risk, screening does not always occur owing to factors such as limited time, uncertainty about which professional should handle it, and a lack of historical weight data for older individuals [38]. This often results in undernutrition being overlooked and only coming to clinicians' attention when it becomes very evident and has likely already affected patients' cognitive status.

In the context of the collaborative PROMED-COG pooled cohorts study, data from two Italian observational studies (ILSA and Pro.V.A.) were harmonized and pooled, yielding a large population-based sample with significant statistical power. This aggregation was enabled by methodological consistency between the two studies, which facilitated their comparability. Specifically, these studies share similar characteristics, including the geographic area of participant recruitment (Italy), the method of data collection (administered by trained interviewers), and the population-based community-dwelling setting. Additionally, both studies are prospective in design, meaning that nutritional status and dietary habits were assessed before the development of outcomes, thereby minimizing recall bias, selection bias, and reverse causation.

However, our study also presents significant limitations. First, as a retrospective study using existing cohort data, the sample size was determined by data availability rather than a specific calculation. Despite this, the large sample size ($n = 3852$) and adequate representation across the identified trajectories provided sufficient statistical power to evaluate the associations. Second, active data collection in both cohorts occurred more than 20 y ago, suggesting that the participants may not be fully representative of the current

older population. Nevertheless, malnutrition remains a persistent health issue among older adults. Although recent global estimates indicate a slight decline in overall prevalence over the past three decades, the absolute number of affected individuals has increased markedly, and a growing burden has been observed in high-income regions such as Western Europe [43]. This pattern likely reflects demographic and epidemiologic changes, including population aging and longer survival among frail individuals, which have expanded the pool of older adults at risk. Although the overall scenario has changed, monitoring nutritional status remains important, as undernutrition is a modifiable factor with potential implications for late-life cognitive health. Therefore, although the specific prevalence rates observed in our study may not precisely reflect current figures, the biological relationship between undernutrition and cognitive decline is likely to remain relevant and potentially of increasing importance considering the aging demographic trends. Additionally, there remains some heterogeneity between the two studies in their design and implementation, including study aims, sampling frames, recruitment procedures, and data collection methods. Moreover, because a complete baseline evaluation of physical activity levels was lacking in the ILSA, walking ability was used as a proxy for mobility, which was also available in the Pro.V.A. An important limitation is related to the exclusion of participants with missing data, who, compared with the analytical sample, were older and more highly educated but showed a higher prevalence of diabetes, CVD, depressive symptoms, and walking disability, with implications for both internal and external validity. Overall, this picture suggests that our analytical sample may be healthier and potentially less representative of the most vulnerable older adults, including those who are institutionalized. As a result, the generalizability of our findings to frail and clinically complex populations, who were underrepresented in our sample, may be limited. However, this issue is more likely to have attenuated rather than inflated the strength of the observed association between undernutrition and cognitive decline, potentially leading to an underestimation of the magnitude of the effect size and to trajectory patterns skewed toward healthier cognitive profiles. Multiple imputation analysis was performed under the missing at random assumption, whereby missingness was modeled as a function of observed covariates. Nevertheless, we cannot exclude that data were missing not at random, and in this case residual bias may persist. However, the results from the multiple imputation sensitivity analysis were consistent with the complete case analysis, supporting the robustness of the main findings.

Another methodological consideration is related to the use of age- and sex-specific median values to define cutoffs for inflammatory and nutritional biomarkers included in the GLIM etiologic criteria. This distribution-based approach may reduce clinical interpretability compared with commonly used clinical cutoffs; however, sensitivity analyses considering commonly adopted clinical cutoffs yielded consistent results, supporting the robustness of the main findings.

Another relevant limitation concerns the assessment of cognitive function using the MMSE. Although widely used in epidemiologic research, routine clinical practice, and national dementia guidelines, the MMSE is a global cognitive screening tool with limited sensitivity to subtle cognitive alterations and domain-specific impairments [44]. However, in the present study, the MMSE was not used for diagnostic purposes but rather as a standardized global measure to model longitudinal trajectories of cognitive change. Nevertheless, future studies incorporating more comprehensive, domain-specific neuropsychological assessments would be valuable for further clarifying the relationship between undernutrition and cognitive decline. Finally, we cannot exclude the

possibility of differential control for confounders between the two studies, as variables unrelated to nutritional status varied between them. Nonetheless, to minimize between-study heterogeneity resulting from the modeling of potentially confounding variables, we standardized the confounders selected for inclusion in the statistical models and their categorization. An important limitation is the inability to establish causality from observational data. Although the prospective design, in which nutritional assessment precedes cognitive outcomes, strengthens temporal interpretation, we cannot exclude reverse causation or bidirectional relationships between undernutrition and cognitive function.

Conclusions

Despite the aforementioned limitations, we believe this study is a valuable resource for understanding the longitudinal association between undernutrition and trajectories of cognitive function in aging, providing significant clinical insights. Health care professionals should therefore carefully assess the nutritional status of older adults, paying particular attention to phenotypic indicators of undernutrition. In fact, nutritional assessment should be an integral part of the multidimensional evaluation of older individuals. Identifying undernutrition can help clinicians detect individuals at increased risk of cognitive decline and monitor them closely over time. Although the observational nature of our study does not allow us to confirm that addressing undernutrition can prevent cognitive decline, the strong associations observed support the importance of nutritional assessment to target this and other modifiable factors and promote healthy aging.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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