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Undernutrition, cognitive decline and dementia: The collaborative PROMED-COG pooled cohorts study

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ABSTRACT

Background & aims: Undernutrition may negatively impact cognitive function, but evidence of this relationship is not yet consolidated. Under the "PROtein enriched MEDiterranean diet to combat undernutrition and promote healthy neuroCOGnitive ageing" (PROMED-COG) project, we evaluated the association between undernutrition, and cognitive decline and incident dementia in older adults.

Methods: Retrospective data harmonization was performed on three Italian population-based studies: the Italian Longitudinal Study of Ageing (ILSA), the Progetto Veneto Anziani (Pro.V.A.), and the Bollate Eye Study-Follow-Up (BEST-FU). The associations between undernutrition, operationalized using the Global Leadership Initiative on Malnutrition (GLIM) criteria, and decline on the Mini-Mental State Examination (MMSE) or dementia incidence follow-up were evaluated with Cox proportional hazard regression models.

Results: The pooled cohort comprised 9071 individuals (52% females) aged between 42 and 101 years. The prevalence of undernutrition at the baseline was 14.3%, significantly higher among females (15.4% vs 13%) and in older age, ranging from 3.5% in those aged <60 years to 28.8% in those 85+ years. Undernutrition was associated with both cognitive decline over a median 8.3-year follow-up (Hazard Ratio (HR) 1.20, 95% Confidence Interval (CI) 1.02–1.41, p = 0.028) and incidence of dementia over a median 8.6-year follow-up (HR = 1.57, 95%CI 1.01–2.43, p = 0.046). For cognitive decline, the association with undernutrition was more marked in males than females (HR = 1.36, 95%CI 1.05–1.77, p = 0.019 vs HR = 1.10, 95% CI 0.89–1.36, p = 0.375).

Conclusion: Undernutrition is prevalent among older people and is associated with an increased risk of experiencing cognitive decline and dementia. The prevention and early identification of undernutrition could be an important nonpharmacologic strategy to counteract neurodegeneration.

1. Introduction

Aging is the biological result of a multitude of molecular and cellular damage accumulated over time. This process is highly heterogeneous and may result in a progressive decline in physical and cognitive functions as well as an increased risk of diseases, including cognitive impairment and dementia [1]. Adopting

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strategies to help older people stay healthy and free from disabilities for as long as possible is, therefore, a crucial priority.

Undernutrition has been defined by the European Society for Clinical Nutrition and Metabolism as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (reduction in lean mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from diseases" [2]. This condition is common in older people due to problems related to low appetite, difficulties in eating, psychological distress, decreased mobility, and limited access to social and health services [3]. Accordingly, recent systematic reviews and meta-analyses showed prevalence of undernutrition in adult or older people living in the community ranging from 3.1% to 17% [4,5] depending on the age group considered or tools used to assess nutritional status.

In addition to the risk of falls and frailty [6], institutionalization [7], and mortality [8,9], previous studies have shown that undernutrition may be associated with an increased risk of cognitive decline and dementia [10–13]. However, the evidence for this relationship is not yet consolidated, mainly due to the heterogeneity of previous studies in defining undernutrition. In particular, most researchers used screening tools such as the Mini Nutritional Assessment (MNA) [11,12,14,15] or single aspects related to undernutrition [13], whereas the last criteria proposed by the Global Leadership Initiative on Malnutrition (GLIM) suggest that the diagnosis of this condition should be supported by both phenotypic and etiologic factors [2]. Phenotypic criteria refer to reduced body weight or muscle mass, and weight loss, while etiologic factors include conditions associated with decreased food intake or assimilation or chronic inflammatory status. To our knowledge, only one study has evaluated whether undernutrition, according to the GLIM criteria, is associated with cognitive and functional decline in individuals diagnosed with dementia. The authors reported that undernutrition could predict the extent to which individuals declined functionally but not cognitively [16]. However, to date, there is no evidence of an association between undernutrition, according to the latter definition and cognitive impairment in community-dwelling individuals.

The "PROtein enriched MEDiterranean diet to combat undernutrition and promote healthy neuroCOGnitive ageing" (PROMED-COG) project aims to better understand the benefits of tackling undernutrition for healthy neurocognitive ageing, and to stimulate collaboration on nutrition and neurocognitive ageing research across Europe [17]. In this context, it is essential to assess and quantify the extent to which undernutrition can influence cognitive deterioration in older age.

Based on the hypothesis that undernutrition may accelerate cognitive decline in community-dwelling individuals, the objective of our study was to evaluate the association of undernutrition, as defined according to the latest GLIM criteria, with cognitive decline and dementia development in advanced age. To this end, we harmonized data from three population-based cohorts to evaluate the study aim in a larger epidemiological sample.

2. Material and methods

2.1. Study population

The analytical sample derived from three population-based studies briefly outlined below.

1) *The Italian Longitudinal Study of Ageing (ILSA* [18]), is a population-based longitudinal study involving a random sample of 5632 individuals aged 65–84 years in 1992–93 (baseline) identified from the population registers of eight municipalities in Northern, Central and Southern Italy. Follow-up examinations were performed in 1995-96 and 2000–01. The survey was performed in two phases. The first phase, administered to all participants, included a personal interview on sociodemographic characteristics, education, occupation, weight and weight history, age at menopause for women, diet, alcohol consumption, smoking habits, information on signs and symptoms of specific investigated diseases (hypertension, myocardial infarction, angina pectoris, cardiac arrhythmia, congestive heart failure, intermittent claudication, diabetes mellitus, stroke, dementia, Parkisonisms, peripheral neuropathy), and on family and medical history. Additionally, laboratory tests, physical examinations, and selected diagnostic tests were performed. Only participants who screened positive for any of the conditions investigated in the first phase were included in the second phase, which consisted of the clinical confirmation by a specialist of suspected cases of diabetes and cardiovascular and neurological diseases.
2) *The Progetto Veneto Anziani (Pro.V.A* [19]) is a longitudinal study based on an age- and sex-stratified random sample of 3099 adults aged ≥65 years, living in Northern Italy. The baseline evaluation was carried out in 1995–97, with follow-up assessments in 1999–2000 and 2002–04. A passive follow-up using regional health registers to derive hospitalization and mortality data was recently performed until 2018. All participants underwent a comprehensive assessment at the local participating hospital or at home (for those who unable to move to the research site) by trained nurses/physicians who assessed sociodemographic characteristics, cognitive performance, dietary intake, disease symptoms, nutritional and functional status. They also underwent a comprehensive physical examination by a nurse and a physician, and blood samples were taken.
3) *The Italian Bollate Eye Study - Follow-Up ((BEST-FU* [20]) is a longitudinal study of 1693 dementia-free community-dwelling individuals from the Lombardy region, Northern Italy, aged 40–74 years. The baseline assessment was performed in 1992–93, and the incidence of dementia during a 20-year follow-up was assessed using electronic health records. At the baseline, individuals underwent a clinical examination to assess their sociodemographic, lifestyle, and medical history. A detailed assessment of their nutritional status was carried out, blood pressure was measured, and fasting blood was taken for biochemical analysis.

The studies protocols were conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures were approved by responsible Ethics Committees (for the ILSA study, by the Institutional Review Board of the eight participating municipalities; for the Pro.V.A. study, the Ethics Committees of the University of Padova and of the nrs. 15 and 18 Local Health Units of the Veneto Region approved the protocol; for the BEST-FU study, by the Ethical Review Board of the National Research Council of Segrate, MI). Written informed consent was obtained from all individuals in the original ILSA and Pro.V.A. while verbal informed consent was witnessed and formally recorded for the BEST-FU study.

For the purposes of the present study, we excluded individuals living in nursing homes (n = 118 enrolled in the Pro.V.A. study, and n = 57 in the ILSA study) and those with missing data on the main exposure and outcome variables (n = 1089, from the ILSA study), resulting in a final pooled sample of 9071 community-dwelling individuals (Supplementary Fig. 1). Missing values for the ILSA study are due to the fact that some scales were administered during the clinical evaluation (Q3) of the screening assessment, after the personal interview (Q1) and the nurse visit (Q2) [18]; as some

subjects withdrew from the study between Q1 and Q3, their Mini-Mental State Examination (MMSE) was not available and their assessment of dementia could not be performed. In light of the differences in the time and sites of enrolment, we can rule out the possibility that some individuals participated in more than one of the above-described studies.

2.2. Data harmonization

Retrospective data harmonisation was performed in accordance with guidelines [21]. Seven variables domains of interest were defined as follow.

1) General information (participant's ID, baseline date, follow-up dates);
2) sociodemographic characteristics (sex, birth date, education, work done for most of the time [categorized into blue collars, white collars, housewives [22]]), marital status). A further harmonized variable related to socioeconomic status (SES) was defined considering education (primary school 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 [23,24]); a composite SES measure was created to incorporate the summed scores for educational attainment and occupation. Total score of 1,2 corresponded to SES = 1 (low); total score of 3 corresponded to SES = 2 (medium); total score of 4 corresponded to SES = 3 (high).
3) variables related to GLIM phenotypic criteria [2] (weight at the study baseline, body mass index [BMI], waist circumference, hip circumference, mid-arm circumference, weight loss in the last year);
4) variables related to GLIM etiologic criteria, including bowel or stomach diseases, liver or gallbladder diseases, chronic bronchitis or emphysema or asthma, cancer, bone or joint diseases, heart failure, blood tests (considering albumin, fibrinogen, white blood cell count, lymphocytes, neutrophils, eosinophils, monocytes, and basophils);
5) lifestyle characteristics, including smoking habit (categorized as current, former, or never), alcohol consumption, categorized as none, light (<7 AU/week for females; <14 AU/week for males), and heavy (≥7 AU/week for females; ≥14 AU/week for males), and engagement in at least 4 h per week of physical activity (derived from frequency questionnaires on leisure activities, available only for the Pro.V.A. and BEST studies).
6) cardio-metabolic factors and other health-related variables (hypertension, diabetes, hyperlipidemia, cardiovascular diseases - CVD, including angina, ischaemic heart disease, arrhythmia, peripheral artery disease, stroke), depressive symptoms, mobility limitation;
7) cognitive impairment and decline, and dementia (Mini-Mental State Examination -MMSE [25] at baseline and the follow-up; diagnosis of dementia at baseline and follow-up).

2.3. Exposure

Undernutrition was operationalized considering the GLIM criteria for the presence of at least one phenotypic criterion and at least one etiologic criterion. Phenotypic criteria included weight loss >5 kg in the last year, low BMI (<20 kg/m^2 if < 70 years or <22 kg/m^2 if ≥ 70 years), reduced muscle mass defined considering mid-arm circumference by age and sex classes [26]. Etiologic criteria included reduced food assimilation (any chronic gastrointestinal condition affecting food assimilation or absorption: bowel or stomach diseases, liver or gallbladder diseases), and inflammation (acute disease/injury or chronic disease-related: malignancy, chronic obstructive pulmonary disease, bone or joint disease, congestive heart failure, albumin < median values by age and sex; fibrinogen, white blood cell count ≥ median values by age and sex).

2.4. Outcomes

As a measure of cognitive function, we considered MMSE, which was assessed both for the Pro.V.A. (baseline, 4- and 7-year follow-up) and ILSA (baseline, 3- and 8-year follow-up) studies. Cognitive impairment was defined at the baseline as a MMSE score one standard deviation (SD) below the population mean value. This operationalization was performed to account for possible population-specific differences in cognitive performance between the two study populations and detect individuals with lower cognitive function [27–29]. Cognitive decline was defined as a change in MMSE score (unadjusted) from the baseline to follow-up, to the worst 25% of the distribution of change for the whole sample.

For the ILSA study, dementia variables were available at baseline and follow-up, whereas for the BEST-FU study (which enrolled only dementia-free community-dwelling subjects) dementia was available at follow-up. For the ILSA study, the dementia variable was based on clinical diagnosis (DSM III-R criteria for the dementia syndrome [30], the NINCDS-ADRDA criteria for possible and probable Alzheimer's disease (AD [31]), the ICD-10 criteria for vascular dementia and other dementing diseases [32]. For the Pro.V.A. study, hospital discharge records (ICD-9 codes) and causes of death (ICD-9 codes) were used to identify participants with dementia. For the BEST-FU study, an algorithm based on a deterministic record linkage between the baseline cohort and the regional pharmaceutical prescriptions registry (ATC), hospital discharge registry (ICD-9/10), mortality registry (ICD-9/10) and drug reimbursement registry (exemption code) was used to identify the presence of dementia [20].

2.5. Statistical analysis

Continuous variables were summarized as mean and SD, or median and interquartile range (IQR), while categorical variables were presented as counts and percentages. Normal distributions of continuous variables were tested using the Shapiro–Wilk test.

Harmonized variables were compared across cohorts using chi-squared or Fisher exact tests for categorical variables and generalized linear models after testing for homoscedasticity (Levene test) or Wilcoxon rank-sum test for continuous variables.

Baseline characteristics of the overall pooled cohort were compared by the presence of cognitive impairment or dementia, cognitive decline during the follow-up, and incident dementia.

The associations between undernutrition at the baseline and cognitive decline (change in MMSE score to the worst 25% of the distribution of change for the whole sample) or dementia incidence during follow-up were evaluated using Cox proportional hazards regression models using time to event as time-scale (further details in Supplementary Materials). The proportional hazards assumption was verified considering Schoenfeld's residuals of the covariates. Models were adjusted for sex, age (continuous), educational level, work done most of the time, marital status, smoking habits, alcohol consumption, diabetes, hyperlipidemia, CVD, depressive symptoms, and mobility limitation.

The analysis assessing cognitive decline included data from 4300 Pro.V.A. and ILSA participants who had at least two MMSE measurements during the observation period. The analysis assessing the risk of dementia included data from 5905 participants in the three cohorts who were free from dementia at baseline and

had available data on the study outcome. As sensitivity analyses, we repeated the Cox regressions after excluding those younger than 65 years (only for the analysis with dementia as outcome), considering age at the event as time and including physical activity level (available only for the BEST-FU and Pro.V.A. studies). Missing values were not imputed in primary analysis. Sensitivity analyses considering multiple imputations of confounders with missing data based on the fully conditional specification method (FCS) were also evaluated [33]; variables considered in the models included educational level, work done most of the time, marital status, smoking habits, alcohol consumption, diabetes, hyperlipidemia, CVD, depressive symptoms, and mobility limitation, and 30 imputed data sets were created and then combined using Proc MI Analyze.

Finally, we evaluated the multiplicative interaction between undernutrition and sex and the independent association of the GLIM components (phenotypic and etiologic criteria) with the study outcomes.

Two-tail p-values <0.05 were considered statistically significant. The analyses were performed using SAS statistical package, release 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Characteristics of the pooled cohort

The pooled cohort comprised 9071 individuals (52% females) aged between 42 and 101 years, whose main characteristics are presented in Table 1. The mean age of the sample was 71.9 (SD 9.9) years and was significantly lower in the BEST-FU (59.6, SD 7.9 years) than in the Pro.V.A. and ILSA studies (76.0, SD 7.7 years, and 74.7, SD 5.7 years, respectively). There were substantial differences between the original studies in terms of educational and socioeconomic levels (lower in the Pro.V.A. cohort), marital status (with a higher proportion of widowed individuals in the Pro.V.A. and ILSA studies), and previous/current occupation (with the highest frequency of white collars workers among the BEST-FU participants). Concerning risk behaviors, both current or former smoking habits and alcohol consumption were more prevalent among individuals enrolled in the BEST-FU study, followed by the ILSA and Pro.V.A. cohorts. The prevalence of CVD increased from the BEST-FU (13.5%) to the Pro.V.A. (30.5%) and ILSA (40.3%), as did the prevalence of depressive symptoms (2.9%, 33.1% and 40.6%, respectively).

3.2. Description of exposure and outcomes

The prevalence of undernutrition according to the GLIM criteria was 14.3% in the pooled cohort, significantly higher among females (15.4% vs 13% in males, p = 0.001), and with increasing age, ranging from 3.5% in those aged <60 years to 28.8% in those aged 85+ years (p < 0.0001 for trend) (Fig. 1). The characteristics used to detect undernutrition at baseline according to the GLIM criteria in the pooled cohort and single studies are shown in Supplementary Table 1. In general, undernourished participants with respect to those not undernourished were older (76.5 ± 8.0 vs 71.1 ± 9.9, p < 0.0001), more often females (55.8% vs 50.9%, p = 0.0013),

Table 1
Baseline characteristics, by study cohort.

	Overall cohort (n = 9071)	BEST-FU (n = 1604)	Pro.V.A. (n = 2981)	ILSA (n = 4486)	p-value
Age (years), range	42–101	42–74	65–101	65–85	
Age, mean ± SD	71.9 ± 9.9	59.6 ± 7.9	76.0 ± 7.7	74.7 ± 5.7	<0.0001
Sex, female, n (%)	4678 (51.6)	738 (46.0)	1762 (59.1)	2178 (48.6)	<0.0001
Education, n (%)					<0.0001
Primary school or less	6684 (74.4)	920 (57.4)	2615 (88.0)	3149 (71.4)	
Middle school	1265 (14.1)	494 (30.8)	212 (7.1)	559 (12.7)	
High school	703 (7.8)	161 (10.0)	96 (3.2)	446 (10.1)	
University or higher	335 (3.7)	29 (1.8)	49 (1.7)	257 (5.8)	
Work done for most of the time, n (%)					<0.0001
Housewife	1333 (15.1)	107 (6.7)	357 (12.1)	869 (20.4)	
Blue collar	4792 (54.4)	859 (53.5)	1794 (60.9)	2139 (50.2)	
White collar	2682 (30.5)	638 (39.8)	794 (27.0)	1250 (29.4)	
Marital status, n (%)					<0.0001
Single or never married	600 (6.6)	59 (3.7)	227 (7.6)	314 (7.1)	
Married or cohabiting	5553 (61.4)	1364 (85.0)	1536 (51.5)	2653 (59.5)	
Separated or divorced	91 (1.1)	27 (1.7)	16 (0.5)	48 (1.1)	
Widowed	2796 (30.9)	154 (9.6)	1201 (40.3)	1441 (32.3)	
SES, n (%)					<0.0001
Low	6210 868.7)	962 (60.0)	2171 (72.9)	3077 (69.1)	
Medium	1930 (21.4)	456 (28.4)	679 (22.8)	795 (17.9)	
High	895 (9.9)	186 (11.6)	130 (4.4)	579 (13.0)	
Smoking status, n (%)					<0.0001
Current smoker	1670 (18.5)	793 (49.4)	264 (8.9)	613 (13.8)	
Former smoker	2785 (30.9)	382 (23.8)	892 (29.9)	1511 (34.1)	
Never smoker	4563 (50.6)	429 (26.8)	1824 (61.2)	2310 (52.1)	
Alcohol consumption, n (%)					<0.0001
Heavy consumer	1577 (17.5)	274 (17.2)	364 (12.2)	939 (21.2)	
Light consumer	3172 (35.3)	1013 (63.6)	531 (17.8)	1628 (36.8)	
No consumer	4249 (47.2)	306 (19.2)	2086 (70.0)	1857 (42.0)	
Cardiometabolic factors and other health status variables					
Hypertension, n (%)	5831 (64.7)	955 (59.5)	2221 (74.6)	2655 (59.9)	<0.0001
Diabetes, n (%)	1191 (13.2)	126 (7.9)	488 (16.4)	577 (13.0)	<0.0001
Hyperlipidemia, n (%)	2663 (31.2)	339 (22.1)	1005 (37.2)	1319 (30.8)	<0.0001
CVD, n (%)	2702 (33.7)	207 (13.5)	809 (30.5)	1531 (40.3)	<0.0001
Depressive symptoms, n (%)	2231 (30.3)	43 (2.9)	896 (33.1)	1292 (40.6)	<0.0001
Mobility limitations, cannot walk, n (%)	324 (5.4)	na	243 (8.2)	81 (2.7)	<0.0001
Cognitive status					
MMSE at T0, mean ± SD	24.9 ± 4.6	na	23.7 ± 5.2	26.0 ± 3.6	<0.0001

Abbreviations: CVD, cardiovascular diseases; MMSE, Mini-Mental State Examination; SES, Socio-Economic Status; na, variable not available.

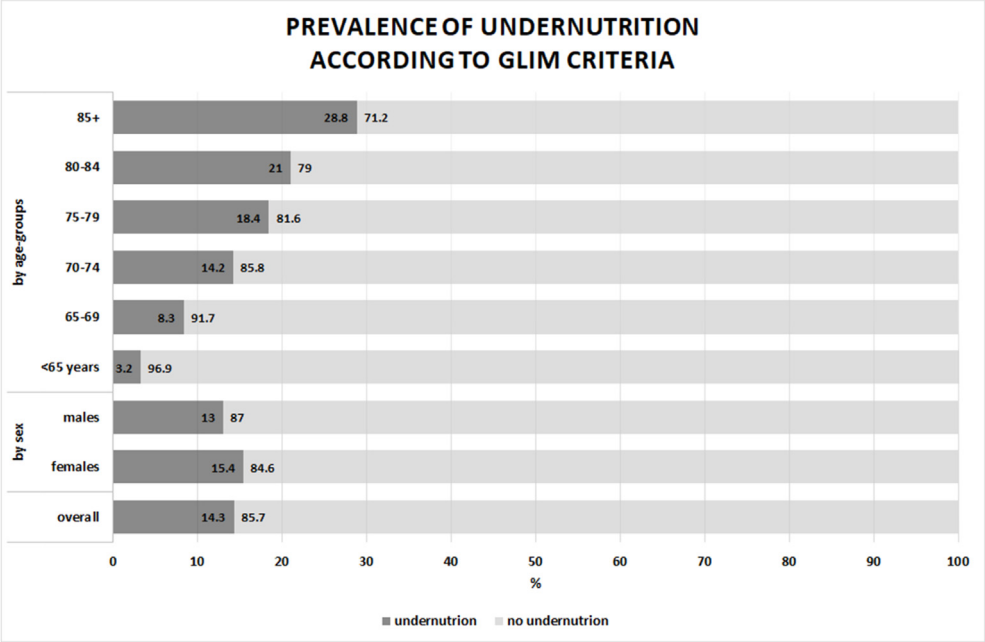

Fig. 1. Baseline prevalence of undernutrition in the pooled cohort.
Notes: The dark gray bars represent the prevalence (%) of undernutrition, and the light grey bars the prevalence of no undernutrition in the overall population, and then stratifying participants by sex and age-groups.

reported a lower education (78.7% had primary school vs 73.6%, p = 0.0022), had more frequently CVD, depressive symptoms and mobility limitation, and obtained a lower score at the MMSE (23.8 ± 5.3 vs 25.1 ± 4.4, p < 0.0001; Supplementary Table 2).

Data on cognitive impairment and cognitive decline were only available for Pro.V.A. and ILSA studies. At baseline, the mean MMSE score was 24.9 (SD 4.6), and 296 (3.7%) participants had a diagnosis of cognitive impairment or dementia. Individuals with cognitive impairment were significantly older, more likely to be females, and less educated than those without cognitive impairment. They also had a higher prevalence of hypertension, diabetes, CVD, depressive symptoms, and mobility limitations (data not shown). Cognitive decline during a median of follow-uo of 8.3-years, defined as a change in MMSE score into the worst 25% of the distribution, was observed in 1316 out of the 4300 participants with available data (30.6%), with a higher prevalence in females than in males (33.1% vs 27.6%, p = 0.0001), and in the oldest age groups (from 20.2% for 65–69 years to 71.6% for 85+ years, p < 0.0001 for trend). Those experiencing cognitive decline were more likely to be males and older, have lower educational level, and lower frequencies of risk behaviors, mobility limitations, and depressive symptoms compared with those free from cognitive decline (Supplementary Table 3). Similarly, participants who developed dementia during the median of 8.6-years of follow-up (n = 249) were more likely to be older, widowed and to have a lower educational and mobility; moreover, this group also had a higher prevalence of CVD and depressive symptoms compared with those who were not diagnosed with dementia (Supplementary Table 4).

3.3. Association of undernutrition with cognitive decline and incident dementia

There were significant differences in MMSE changes during the follow-up between undernourished and non-undernourished participants, with the former showing a greater decline (Fig. 2). In particular, the MMSE loss from baseline to the first follow-up increased by 71.9% in the undernourished participants. The increased MMSE decline linked to undernutrition was more marked in males (+256.3% vs +33.3% in females), and in septuagenarians (65–69 years + 36.4%, 70–74 years + 104.3%, 75–79 years + 83.3%, 80+ years +17.5%).

In the adjusted Cox proportional hazards model, undernutrition at baseline was significantly associated with cognitive decline on the MMSE (Hazard Ratio [HR] = 1.20, 95% Confidence Interval [CI] 1.02–1.41), and the result was more pronounced in males (HR = 1.36, 95% CI 1.05–1.77) than in females (HR = 1.10, 95% CI 0.89–1.36) (Table 2 and Supplementary Table 5). Results were confirmed when considering models with multiple imputations for the missing data on the confounders (Supplementary Table 6). When the components of undernutrition were considered separately, the phenotypic (HR = 1.19, 95% CI 1.01–1.39) but not the etiologic criterion (HR = 1.10, 95% CI 0.75–1.60) was associated with cognitive decline.

Incident dementia was recorded in 249 participants (4.2%), with no differences by sex (4.4% among females vs 4.0% among males, respectively; p = 0.400) (Supplementary Table 4). Undernutrition at the baseline was significantly associated with incident dementia (HR = 1.57, 95% CI 1.01–2.43) (Table 2); the results were confirmed when considering only participants aged 65 years or more (HR = 1.56, 95% CI 1.00–2.43). The main driver of the association between undernutrition and dementia incidence seemed to be related to the phenotypic component (HR = 1.50, 95% CI 0.98–2.34; for the etiologic component HR = 1.09, 95% CI 0.34–3.51). When the analyses were stratified by sex, the associations between undernutrition and dementia incidence were not significant for both males and females (HR = 1.72, 95% CI 0.89–3.36 for males; HR = 1.56, 95% CI 0.86–2.83 for females), possibly due to the small sample size (Supplementary Table 5). Similarly, the association with dementia incidence was attenuated and not significant when age at the event was considered as time and physical activity level was added to the model (Supplementary Table 7), or when analyses were repeated after multiple imputation for missing data of the confounders (Supplementary Table 6).

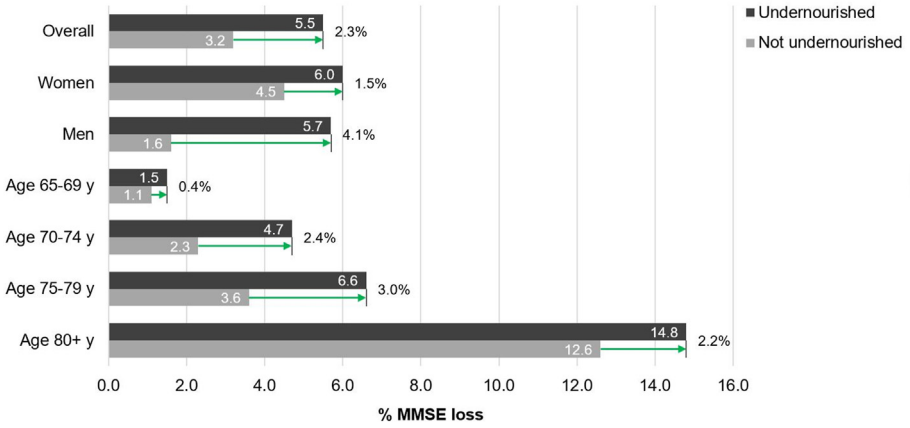

Fig. 2. Differences in MMSE scores during the follow-up between undernourished and not undernourished participants according to GLIM criteria.
Notes. The green arrow and percentage indicate the % change in MMSE between undernourished and non-undernourished participants (score for undernourished − score for not undernourished participants)/(score for not undernourished participants). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Cox regression for the association of undernutrition with cognitive decline and incident dementia.

	Cognitive decline (n = 3267)		Dementia incidence (n = 3219)	
	N. events, person-years	HR (95% CI)	N. events, person-years	HR (95% CI)
No undernutrition	1078, 20484.5	[ref]	197, 48106.8	[ref]
Undernutrition	231, 3281.5	1.20 (1.02–1.41)	48, 4559.2	1.57 (1.01–2.43)

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio. Models are adjusted for sex, age (continuous), educational level, work done most of the time, marital status, smoking habits, alcohol consumption, diabetes, hyperlipidemia, cardiovascular diseases, depressive symptoms, and mobility limitation. *Notes*: Participants with missing data on the covariates were excluded from the model.

4. Discussion

Our study confirms that undernutrition, defined based on the last international GLIM criteria, is prevalent among older people, affecting almost one out of three individuals aged over 85. This finding aligns with previous reports on the same topic, which considered community-dwelling individuals [34,35]. When exploring the association between undernutrition and cognitive health, we found that undernourished individuals, especially males, had a 20% increased risk of experiencing cognitive decline and a 57% higher risk of incident dementia.

The relationship between nutritional and cognitive status is well-known, and, in keeping with our findings, previous studies have demonstrated that poorer nutritional status can increase the risk of a faster cognitive worsening or dementia development [36]. However, compared with ours, most of these studies used a single screening tool or a cross-sectional design or were performed in different countries, which may explain possible discrepancies in the prevalence of malnutrition and the results from multivariate analyses. For instance, in a Greek study on 2092 men and women, the authors found that 35.0% were at risk of malnutrition (measured using the MNA), and 11.3% were malnourished. In multiple regression analysis, nutritional status was independently associated with cognitive status [11]. In another study of 1248 Taiwanese men, malnutrition, as measured by the MNA (6.1%), increased the odds of functional decline and cognitive improvement after adjustment for age, body mass index, and comorbidities [13]. In a cohort of 2365 individuals, Yu and colleagues reported a prevalence of malnutrition, as measured by the MNA, of 5.54% and, after adjustment for sociodemographic variables, a fourfold increase in the odds of cognitive impairment was observed for malnourished participants [14]. In another cross-sectional Chinese study on 946 centenarians, multivariate analyses showed that the prognostic nutritional index and MNA were positively associated with cognitive deficits and MMSE score [15]. Finally, in a prospective longitudinal study conducted in China, Sun and colleagues reported that among 1632 subjects, 19.4% and 15.6% had mild and moderate to severe malnutrition, assessed through the Geriatric Nutritional Risk Index. Malnourished people had lower MMSE scores after adjustment for confounders [10].

There are multiple possible explanations for this association. Indeed, malnutrition is associated with a reduced capacity to renew and repair tissues, including neurological ones, due to inadequate energy and nutrient intake [37,38]. Moreover, undernutrition is characterized by a dysfunction of the immune system, promoting the establishment of a chronic mild inflammatory status [39], one of the mechanisms that foster neurodegeneration [40]. An emerging role in the development of dementia has also been attributed to alterations in the gut microbiota [41,42], which have recently been linked to both undernutrition and poor appetite [43]. Finally, we cannot rule out the possibility that undernutrition and cognitive decline are part of the same process triggered by common risk factors. For instance, conditions such as depression or other chronic diseases characterized by an inflammatory substrate, as well as lifestyle factors such as sedentarism, have been associated with both the development of undernutrition and dementia [44,45].

The recent introduction of the GLIM criteria as a more comprehensive way of assessing malnutrition, considering both phenotypic and etiologic criteria, allows us to move forward for a deeper understanding of this complex relationship. Some authors found that undernutrition, defined according to the GLIM criteria

was associated with a higher risk of presenting frailty and sarcopenia [46], but, to our knowledge, none has evaluated its impact on cognitive performance over time in community-dwelling individuals. Using the GLIM criteria made it possible to uncover whether phenotypic or etiologic factors were more strongly associated with cognitive decline and incident dementia. Our results show that the phenotypic component was the major driver in the association between undernutrition and cognitive deterioration, while etiologic factors made a non-substantial contribution. These findings support the relevant role that inadequate energy and nutrient intake, resulting in reduced body weight or muscle mass, could play in neurodegeneration. Of note, such phenotypic characteristics may indicate underlying frailty or sarcopenia conditions, which can often coexist with undernutrition, as mentioned above [46], and increase the risk of dementia [47,48]. On the other hand, the lack of a significant relationship between etiologic criteria and cognitive decline or dementia might be justified by the fact that our cohort had a high prevalence of disorders linked with inflammatory status. In addition, assessing only a few markers of systemic inflammation might have limited the evaluation of the etiologic criteria' role in our outcomes [49], which requires further investigations.

Interestingly, the association between undernutrition and cognitive decline was more pronounced in males, and greater MMSE decline over time was also found in the septuagenarians. As far as sex-related differences are concerned, although the prevalence of undernutrition is generally higher in females, its impact on cognitive health seems to be greater in males [50,51]. As emerged by a recent study involving individuals from six continents, although most of factors influenced the risk of dementia in males and females in a similar way, some, such as educational level and previous drinking habit, were more impactful in the male sex [52]. Whether this difference could also involve undernutrition is unclear, as there is still very little evidence on the possible effect modification of sex in the association between undernutrition and dementia risk. However, a certain variability in dietary patterns between males and females may influence the type of undernutrition [50] and, possibly, the impact of this condition on neurodegeneration. Further research on this topic will be of interest in the future. Concerning the fact that the broadest discrepancy in MMSE loss between undernourished and non-undernourished was found in septuagenarians, we hypothesize that the impact of nutritional status on cognitive decline may be more evident when an excessive number of risk factors has not yet been accumulated, as in the youngest old.

Finally, when we did a sensitivity analysis by modelling their risk on an age scale instead of time in the study [53–55], we found that the associations were slightly attenuated and no longer statistically significant. This may be because we were looking at the risk of developing cognitive decline and dementia, which are age-related conditions, meaning that age is a strong confounder of the association between exposure and outcome. Instead, a greater weakening of the association between malnutrition and cognitive decline was observed when including physical activity instead of walking ability as a confounding factor. An explanation for this could be that walking ability is much more related to a disability and, therefore, to the outcome, while we cannot fully assume that people able to walk are consequently physically active. In addition, the association may have lost statistical significance due to the reduction in sample size caused by the exclusion of the ILSA cohort from the analysis.

Regarding the limitations of the present study, it should be considered that our analyses are based on retrospectively harmonized databases. Achieving retrospective harmonization is challenging because it is time-consuming and requires specific technical and scientific expertise [56]. Regarding the PROMED-COG project, one of the main issues related to the harmonization was the heterogeneity of the three datasets under analysis, including the study aims, the selected questionnaires and scales, the target population (the ILSA and Pro.V.A. studies were conducted in older people aged 65 years or more whereas the BEST-FU study was performed in middle-aged individuals), and the follow-up data collection (active for ILSA and Pro.V.A vs passive for the BEST-FU). In order to understand whether variables recorded in different data sources measured the same information and to facilitate the selection of variables to be harmonized, we performed a step-by-step procedure that included access to the documentation of the original studies, discussion with the researchers responsible for each dataset, and preliminary exploration of the dataset before the final harmonization. On the other hand, the three studies were performed in the same setting (community-dwelling individuals) and over the same time period (from 1992 to 1997), fostering the comparison between them. A further limitation concerns the unavailability of data on apolipoprotein E (ApoE) polymorphism in the entire cohort, which made it impossible to evaluate the role of ApoE-ε4 allele as a confounder (by contributing to weight loss, especially in females) or as an effect modifier in the studied association. Finally, the possible underestimation of dementia incidence is worth noting. The prevalence of dementia in industrialized countries is around 8% in people over 65 years of age, rising to over 20% after the age of 80 [57]. In our pooled cohort, we found an overall incidence of 4.2% (4.7 per 1000 person-year), which is lower than previously reported estimates. These data can be partly due to the fact that in both the Pro.V.A. and the BEST-FU study, the diagnosis of incident dementia was based on record linkage with health registries. Although previous research has shown that routinely collected health data with record linkage can provide plausible estimates for dementia prevalence and incidence, underdiagnosis may occur and lead to underestimation of associations with risk/protective factors [58]. Moreover, cognitive decline was defined based on the study populations' distribution of MMSE changes. Although this issue allowed us to identify the individuals who experienced a steeper cognitive deterioration within each population, binary outcome may limit our understanding of the association between undernutrition and cognitive deterioration [59]. In this regard, our future work will deepen this topic by considering different trajectories of cognitive performance over time. Finally, in the present study, we assessed the role of the phenotypic and etiologic criteria on the risk of cognitive decline and dementia but not the impact of the single factors included in these components, which will be a matter of future investigations.

Our study also has some strengths: data harmonization helped to create comparable datasets across the three cohort studies under examination; moreover, the pooling of the datasets allowed for an increase in sample size and more powerful statistical analysis, which would have been less feasible using any of the datasets alone. Furthermore, we evaluated for the first time the association between undernutrition, as defined by the latest GLIM criteria, and cognitive decline and dementia in community-dwelling older individuals using a large epidemiological sample defined by harmonizing data from three population-based cohorts.

5. Conclusion

Undernutrition is a prevalent condition in older adults and is associated with an increased risk of experiencing cognitive decline, especially in males, and of developing dementia. Therefore, the prevention and early detection of undernutrition in adult and older individuals represent steps that physicians should systematically include among the non-pharmacologic strategies to counteract neurodegeneration.

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Author contributions

FP, SC, MN, and CT conceived, designed, and planned the study. MN conducted the statistical analysis. MN, FP and CT prepared the first draft of the manuscript. SC contributed to drafting the manuscript. GS, SM, LB, LCPGMDG, DV, and CTME critically edited and revised the manuscript for important intellectual content. All authors have approved the submitted version and any substantially modified version that involves each author's contribution to the study.

The corresponding author, FP, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.09.001.

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