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Original article

Malnutrition according to ESPEN definition predicts long-term mortality in general older population: Findings from the EPIDOS study-Toulouse cohort

Dolores Sánchez-Rodríguez [a, b, c, d, *], Ester Marco [b, c, e, f], Anne-Marie Schott [g], Yves Rolland [h], Hubert Blain [i], Olga Vázquez-Ibar [a, d], Ferran Escalada [b, c, e], Xavier Duran [j], Josep M. Muniesa [b, c, e], Cédric Annweiler [k, l]

[a] Geriatrics Department, Parc de Salut Mar (Centre Fòrum – Hospital del Mar), Barcelona, Spain
[b] Rehabilitation Research Group, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain
[c] School of Medicine, Universitat Autònoma de Barcelona, Spain
[d] School of Medicine, Universitat Pompeu Fabra, Barcelona, Spain
[e] Physical Medicine and Rehabilitation Department, Parc Salut Mar (Hospital del Mar – Hospital de l'Esperança), Barcelona, Spain
[f] Universitat Internacional de Catalunya, Barcelona, Spain
[g] Department IMER, Lyon University Hospital, EA 4129, RECIF, University of Lyon, Inserm, U831, Lyon, France
[h] Department of Geriatrics, Toulouse University Hospital, Gerontopole of Toulouse, INSERM U1027, University of Toulouse III, Toulouse, France
[i] Department of Internal Medicine and Geriatrics, Montpellier University Hospital, University of Montpellier 1, Montpellier, France
[j] Methodology and Biostatistics Support Unit, Institut Hospital del Mar d'Investigacions Mèdiques, (IMIM), Barcelona, Spain
[k] Department of Neurosciences and Aging, Division of Geriatric Medicine, Angers University Hospital, Angers University Memory Clinic, Research Center on Autonomy and Longevity, UPRES EA 4638, University of Angers, UNAM, Angers, France
[l] Robarts Research Institute, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

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SUMMARY

Background: The European Society of Clinical Nutrition and Metabolism (ESPEN) has developed a consensus definition of malnutrition. This study aimed to determine the prevalence of malnutrition according to the ESPEN definition in otherwise healthy community-dwelling older women and to explore its value for predicting long-term mortality in this population.

Methods: This prospective population-based cohort study included 181 women (age ≥75 years) from a subsample of the EPIDémiologie de l'OStéoporose (EPIDOS) study participants from Toulouse. Inclusion criteria were the availability of the data on variables required to apply the ESPEN definition and survival after 7 years of follow-up. Primary outcome was mortality at 12-year follow-up; main covariates were malnutrition assessment according to the ESPEN consensus and its components (unintentional weight loss, BMI, and FFMI). Body composition was assessed by dual-energy X-ray absorptiometry at baseline and at 7-year follow-up. Kaplan-Meier survival curves and adjusted Cox regressions were performed. Analysis was adjusted for age, hypertension, diabetes mellitus, and coronary heart disease as potential confounders.

Results: Complete data were available for 179 of the 181 women in the EPIDOS-Toulouse cohort (83.1 ± 2.2 years) and 13 (7.3%) fulfilled the ESPEN definition for malnutrition at 7-year follow-up. Malnutrition was associated with increased risk of mortality (adjusted HR = 4.4 [95%CI: 1.7–11.3]). Among the ESPEN components, only BMI was associated with increased mortality (adjusted HR=0.6 [95% CI: 0.4–0.9]).

Conclusions: Although malnutrition prevalence according to the ESPEN definition was relatively low (7.3%) in this sample of otherwise healthy community-dwelling older French women, malnutrition was associated with 4.4-fold higher mortality risk at 12-year follow-up.

Abbreviations: BMI, Body mass index; DEXA, Dual-energy X-ray absorptiometry; EPIDOS, EPIDémiologie de l'OStéoporose study; ESPEN, European Society of Clinical Nutrition and Metabolism; FFM, Fat-free mass; FFMI, Fat-free mass index; ICD, International Classification of Diseases; INSERM, Institut National de la Santé et Recherche Médicale; MMSE, Mini-Mental State Examination; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; WHO, World Health Organization.

* Corresponding author. Geriatrics Department, Parc de Salut Mar (Centre Fòrum – Hospital del Mar), Barcelona, Spain.
E-mail addresses: 97662@parcdesalutmar.cat (D. Sánchez-Rodríguez), anne-marie.schott-pethelaz@chu-lyon.fr (A.-M. Schott), rolland.y@chu-toulouse.fr (Y. Rolland).

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1. Introduction

Malnutrition is an independent prognostic factor for disability [1], hospitalization and readmissions [2], institutionalization [3], and death in the short and medium term [4]. Malnutrition and nutrition-related conditions, such as sarcopenia and frailty, are reversible when effective therapeutic approaches are applied [5,6]. The sooner these interventions are administered, the more benefits are obtained [7]. Therefore, an early identification of older populations at risk might be suggested as a priority in geriatric medicine, with special emphasis in healthy older populations living independently at home who may receive greater benefit in terms of avoiding hospitalization and increasing their years of life free of diseases and better quality of life [7,8].

However, accuracy in malnutrition screening and diagnosis varies depending on the method used and the target population [9]; to date, no single tool has been able to provide an internationally validated nutritional diagnosis in addition to predicting clinical adverse outcomes in the long term [10]. Therefore, malnutrition and nutrition-related conditions often remain underrecognized, underdiagnosed, and undertreated [11,12].

The European Society of Clinical Nutrition and Metabolism (ESPEN) developed a consensus for malnutrition diagnosis, designed to improve the recognition of malnutrition and nutrition-related conditions [5,6], establish prevalence, allow comparisons between settings, and support coding purposes as a diagnosis accepted by the World Health Organization (WHO) and the International Classification of Diseases (ICD) [13]. Given that malnutrition varies in different settings and populations, and that the prognostic value of malnutrition as defined by the ESPEN consensus, has not yet been well established, the present study aimed to determine the prevalence of malnutrition according to the ESPEN consensus in otherwise healthy, community-dwelling, older women from a subsample of the EPIDémiologie de l'OStéoporose study (EPIDOS), the EPIDOS-Toulouse cohort, and to assess its potential value to predict long-term mortality.

2. Methods

2.1. Design

Post-hoc analysis of the EPIDOS-Toulouse study; the EPIDOS is an observational prospective multicenter national cohort designed to evaluate the risk factors for hip fracture among otherwise healthy, community-dwelling, older women in France.

2.2. Participants

From 1992 to 1994, the EPIDOS recruited 7598 women aged 75 years and older from electoral lists in five French cities (Amiens, Lyon, Montpellier, Paris, and Toulouse), excluding those subjects who were not able to walk independently and those with a history of hip fracture or bilateral hip replacement. Sampling and data collection procedures have been described in detail elsewhere [14–16]. Study participants had a full medical examination, which consisted of structured questionnaires, information about chronic diseases, and a clinical examination. Body mass index (BMI) and fat-free mass index (FFMI), variables required to apply the ESPEN definition [5], were only available in a subsample of 179 women of the EPIDOS-Toulouse cohort at 7-year follow-up (Fig. 1).

2.3. Long-term mortality

The main outcome was long-term mortality in the EPIDOS-Toulouse cohort during a 12-year follow-up. Data were collected by phone call and/or a search of the French national death registry, CépiDC [Centre d'épidémiologie sur les causes médicales de décès], up to October 1, 2010; in addition INSERM (Institut National de la Santé et Recherche Médicale) was searched for vital status data in October 2010) [16].

2.4. Malnutrition as defined by the ESPEN consensus

The ESPEN consensus recommends identification of subjects at nutritional risk as a first screening step [6]. The ESPEN criteria offer two alternative ways to diagnose malnutrition: 1) body mass index (BMI) < 18.5 kg/m^2 and 2) unintentional weight loss (>10% in the 7-year follow-up period) combined with age-related BMI (<20 kg/m^2 in patients younger than 70 years and <22 kg/m^2 in those aged ≥70 years) or fat-free mass index (FFMI) (<17 kg/m^2 in men and <15 kg/m^2 in women) [5]. In the present study, fat-free mass (FMM) was assessed by dual-energy X-ray absorptiometry (DEXA) (Lunar DPX-Plus, GE Lunar Corp., Madison, WI) at baseline and after 7 years (1999–2000) of follow-up (QDR 4500 W Hologic, Waltham, MA). Detailed description of characteristics of the DEXA measurements, assessments, and calibration have been published previously [14,17]. FFMI was obtained by dividing the fat-free mass (kg) by the square of the height in meters.

Demographic and clinical characteristics included age, sex, cognitive status (Mini-Mental Status Examination, maximum score = 30), instrumental activities of daily living (IADL) [15], gait

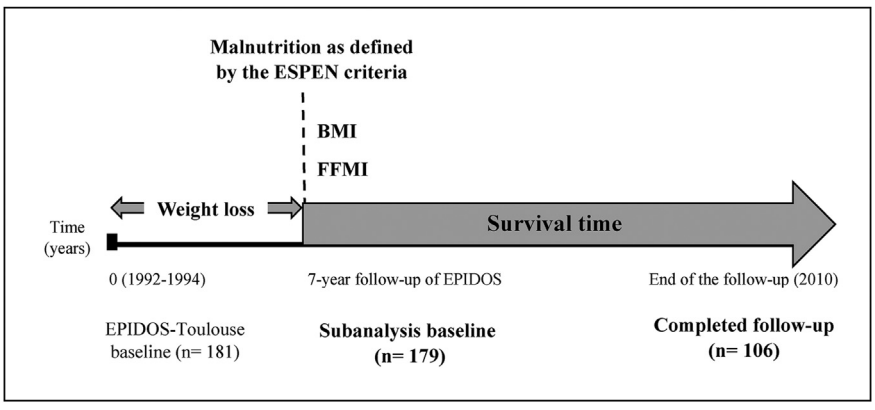

Fig. 1. Timeline of the study: EPIDOS baseline, our subanalysis baseline, and survival time.

speed (in m/s), and presence of hypertension, diabetes mellitus, and coronary heart disease.

National and international research ethics guidelines were followed [18], including the Deontological Code of Ethics, Declaration of Helsinki (1983), and the EPIDOS study was approved by the local ethics committee. All participants gave written informed consent. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for reporting observational research cohorts were followed [19] (See Additional File 1).

2.5. Statistical analysis

Characteristics of quantitative variables were expressed as mean and standard deviation (SD). These characteristics were shown for the whole sample and according to presence of malnutrition. Mann–Whitney was applied to compare quantitative characteristics between the two groups. Analysis of mortality by malnutrition status was assessed first by Kaplan–Meier survival curves. Differences we rechecked with log-rank test followed by crude and adjusted Cox regressions. Adjusted analyses for cognition and function variables were performed. The same analyses were repeated after adjustment for each component of the ESPEN definition (BMI, unintentional weight loss, and FFMI category, using 15 kg/m^2 as cut-off point). All adjusted analyses included age as a confounder, along with hypertension, diabetes mellitus, and coronary heart disease as potential confounders. Proportional hazards assumptions were checked for each model and results were considered statistically significant at p-value < 0.05. Statistical analysis was performed using STATA 15.0 software (Stata Corp.; College Station, Texas, USA).

3. Results

From the 181 otherwise healthy, community-dwelling, older women included in the EPIDOS-Toulouse cohort at baseline, 179 (aged 83.1 ± 2.2 years) met the inclusion criteria for this analysis. Baseline clinical characteristics of the sample are detailed in Table 1. The specific components of the ESPEN definition were applied: 99 women had lost weight; this weight loss was unintentional and >10% in 12 cases (12.1%). Malnourished women did not differ in age, cognitive status, gait speed, and calcium and protein intakes. Thirteen participants (7.3%) fulfilled ESPEN basic diagnosis criteria: 8 (4.5%) had BMI<18.5 kg/m^2, 5 (2.8%) reported unintentional weight loss combined with low age-related BMI, and 6 (3.4%) participants had unintentional weight loss and FFMI < 15 kg/m^2 (Fig. 2). Figure 3 shows the overlap of the malnourished patients according to the specific components of the ESPEN definition.

Mean age of death was 85.9 ± 3.3 years. Survival curves differed significantly between the malnourished and non-malnourished groups (p-value for log-rank test <0.001) (Fig. 4). Mortality was 92.3% in the group of malnourished women (only one of the 13 malnourished women according to ESPEN criteria survived to the end of follow-up), compared to 56.6% mortality in the 166 women without malnutrition (p = 0.016) (Table 1).

A more detailed analysis by proportional hazard models is provided in Table 2. The crude analysis showed a significant increased mortality risk according to malnutrition status as defined by the ESPEN consensus: HR 2.7; 95% CI: 1.5–5.0). Mortality differences were consistent regardless of the adjusted model: HR 4.4 (95% CI: 1.7–11.3) when adjusted for cognition and functioning variables. The multivariate analysis that included the ESPEN components showed an inverse association between mortality and BMI; this association was significant when the components BMI, unintentional weight loss, and FFMI <15 kg/m^{2}were included (HR: 0.6; 95% CI: 0.4–0.9), as well as after adjustment for cognition and function variables (HR: 0.5; 95% CI: 0.3–0.9). In a further step, adjusting these models by hypertension, diabetes mellitus, and coronary heart disease, these results were also consistent, showing a significant association with malnutrition as defined by the ESPEN consensus (Table 3).

4. Discussion

In this post-hoc analysis, use of the ESPEN malnutrition definition to predict long-term mortality in the EPIDOS-Toulouse cohort was associated with a 4.4-fold higher mortality risk in healthy community-dwelling older women, which remained after adjustment for covariables. Results of the present study showed a relatively low prevalence of malnutrition (7.3%) in the EPIDOS-Toulouse cohort, supporting the clinical value of the ESPEN definition of malnutrition as a predictor of long-term mortality in otherwise healthy community-dwelling older women. The observed prevalence of malnutrition agreed with previous studies conducted in geriatric outpatients using the ESPEN consensus definition (6.3%) [20], but was much lower than has been reported in acute diabetic inpatient settings (21%) [3] or in postacute care (19–20%) [21].

The effects of malnutrition and nutrient deficiencies on clinical adverse outcomes and short-term mortality is long-established and well-described in older adults, mainly in patients with comorbidities [3,4,22]. Recent studies have analyzed the capability of the ESPEN definition of malnutrition to predict short-term mortality, reporting a nearly three-fold increased risk of mortality at 6 and 9 months in malnourished patients with chronic obstructive pulmonary disease [22] and in patients discharged from acute geriatric

Table 1
Clinical characteristics of participants (n = 179).

	EPIDOS-Toulouse cohort (n = 179)	Malnutrition (n = 13)	No malnutrition (n = 166)	p-value
Age, years	83.1 ± 2.2	84.2 ± 4.1	83.1 ± 2.8	0.212
MMSE score (/30)	27.7 ± 2.6	27.8 ± 2.3	26.1 ± 5.2	0.547
Body mass index, kg/m^2	24.3 ± 3.7	18.9 ± 2.4	24.8 ± 3.4	**<0.001**
Fat-free mass, kg/m^2	35.1 ± 4	33.2 ± 3.6	35.2 ± 4	0.061
Fat-free mass index, kg/m^2	15.1 ± 1.6	13.7 ± 1.1	15.2 ± 1.5	**<0.001**
Hypertension (n, %)	67 (37.4%)	7 (53.9%)	60 (36.1%)	0.240
Diabetes mellitus (n, %)	6 (3.4%)	0 (0%)	6 (3.6%)	1.000
Coronary heart disease (n, %)	23 (12.9%)	0 (0%)	23 (13.9%)	0.380
Gait speed, m/s	1 ± 0.6	0.9 ± 0.2	1 ± 0.6	0.496
Calcium intake, mg/24h	858.3 ± 267.1	951.9 ± 289.0	851.0 ± 264.9	0.764
Protein intake, mg/kg/24h	67.2 ± 13.8	67.1 ± 14.2	67.2 ± 13.8	0.764
Mortality at 12-year follow-up	106 (59.2%)	12 (92.3%)	94 (56.6%)	**0.016**

MMSE: Mini-Mental State Examination. Data presented as mean ± standard deviation unless otherwise indicate as absolute numbers and percentages. Comparisons between participants with and without malnutrition as defined by ESPEN consensus was based on independent samples *t*-test or Chi-square test, as appropriate; significant p-value (<0.05) indicated in bold.

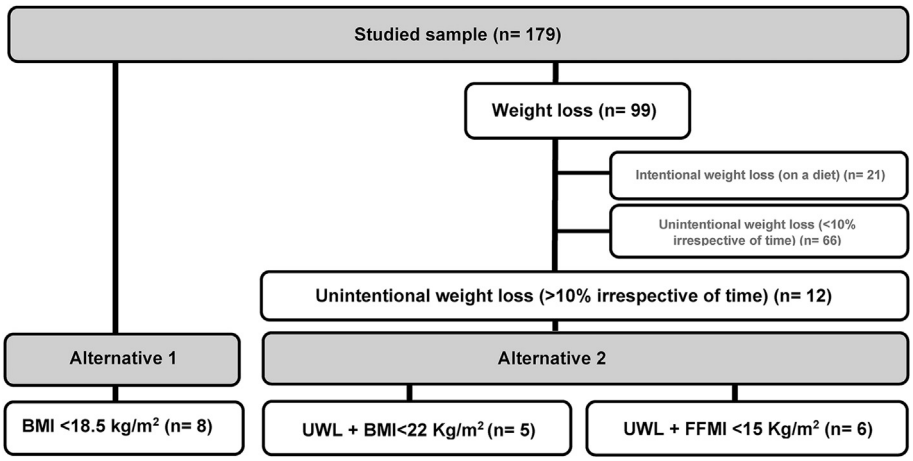

Fig. 2. Malnutrition as defined by the ESPEN consensus in the EPIDOS-Toulouse cohort (n = 179).

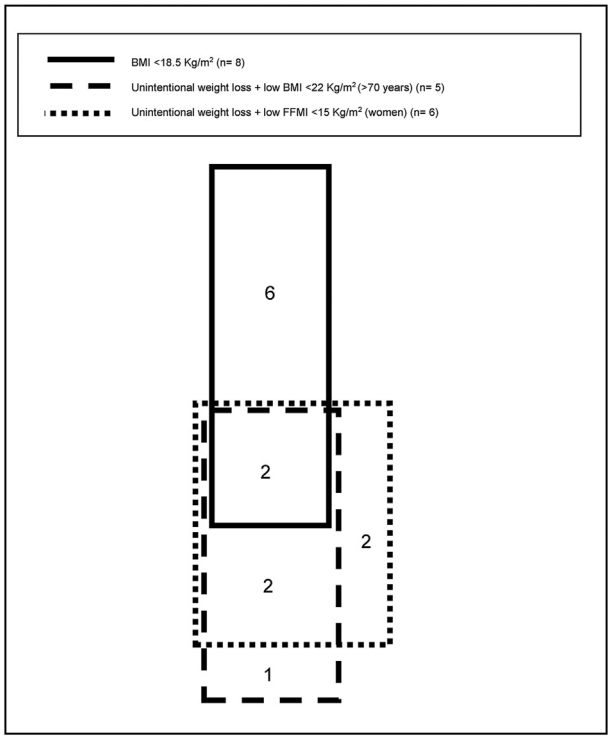

Fig. 3. Overlap of the new ESPEN consensus definition of malnutrition and the individual diagnostic criteria in community-dwelling healthy older women from the EPIDOS-Toulouse cohort (n = 179).

wards [4]. In addition, malnutrition increases the hospital stay and the probability of in-hospital death by a factor of 2.7, and decreases the probability of being discharged home rather than to an institution in acute diabetic older inpatients [3]. Our study adds insight to the association between malnutrition as defined by the ESPEN consensus and mortality over time. To our knowledge, this is the longest follow-up period reported to date, showing 92.3% mortality in malnourished women, significantly higher (p = 0.016) than the 56.6% mortality observed in non-malnourished patients.

The ESPEN consensus includes weight loss among its subscores; this is one of the strongest indicators of health status in older people due to its prognostic value and because it can be easily assessed in all populations worldwide [13]. The scientific community agrees that this indicator is the cornerstone of nutritional assessment, and should be considered independently of the rate, amount, and etiology of weight loss. However, there is a lack of consensus about the exact amount and rate of weight loss that should be defined as the cut-off to indicate clinical implications [13,23]. Our study analyzed time-independent weight loss of >10%, considered relevant for chronic conditions by the ESPEN consensus [5], without considering acute illnesses (due to lack of data). This is a limitation of our study. A predictive value for mortality risk was observed despite using just one of the amounts and time periods of weight loss proposed by the ESPEN consensus [5]. Further analysis of prospective cohorts with a closer follow-up is recommended.

Specifically, we found that only low BMI was associated with long-term mortality. BMI was incorporated into the consensus because its predictive value for mortality is well established [24], as confirmed by the present study results. The controversial relationship between BMI, frailty, and clinical adverse events (falls, hip fractures, hospital admissions, and all-cause mortality) has been recently assessed in the EPIDOS cohort, showing a protective effect of overweight and obesity [25]. This is in line with previous findings from EPIDOS, as lower BMI had been related to mortality in a 17-year follow-up [24]. However, J-shaped (but not linear) relationships between for BMI and higher risk of death also have been described [26]. As BMI is one of the subscores of the ESPEN consensus, further analysis in larger samples may be needed.

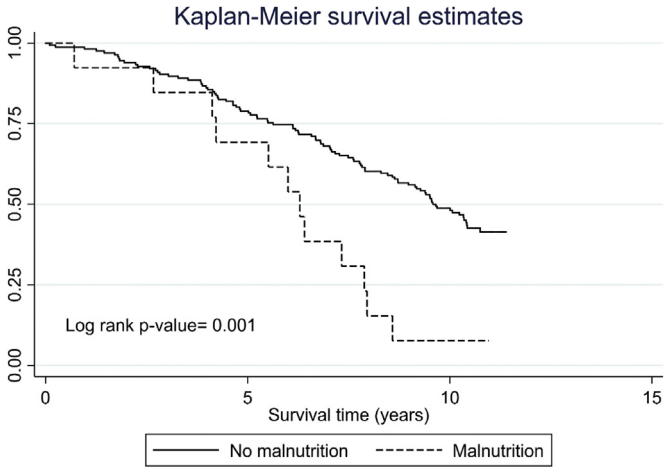

Fig. 4. Survival curve according to malnutrition as defined by the ESPEN criteria.

Table 2
Hazard ratios of mortality (dependent variable) according to malnutrition as defined by the ESPEN consensus and according to its specific components (independent variables) (n = 179).

	Mortality according to ESPEN definition of malnutrition					
	Crude analysis			Adjusted analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Malnutrition as defined by ESPEN consensus	2.7	[1.5 to 5]	**0.001**	4.4	[1.7 to 11.3]	**0.002**
Age				1.1	[1 to 1.2]	0.145
Gait speed				0.9	[0.8 to 1]	0.087
MMSE score				0.2	[0 to 1.3]	0.093
IADL score				0.5	[0.3 to 0.8]	**0.011**
Components of ESPEN definition	**Mortality according to specific components of ESPEN definition of malnutrition**					
	Crude analysis			Adjusted analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Unintentional weight loss	1.4	[0.7 to 2.9]	0.334	2.2	[0.8 to 5.6]	0.108
Body mass index	0.6	[0.4 to 0.9]	**0.029**	0.5	[0.3 to 0.9]	**0.019**
Fat-free mass index <15 kg/m^2	1	[0.6 to 1.5]	0.909	0.8	[0.4 to 1.4]	0.372
Age				1.1	[1 to 1.2]	0.119
Gait speed				0.9	[0.8 to 1]	0.123
MMSE score				0.2	[0 to 1.1]	**0.058**
IADL score				0.4	[0.2 to 0.8]	**0.004**

HR: hazard ratio; CI: Confidence interval; Adjusted analysis: adjustment for age, gait speed at baseline, MMSE at 7-year follow-up, IADL index at 7-year follow-up; significant HR p < 0.05) indicated in bold.

Table 3
Hazard ratios of mortality (dependent variable) according to malnutrition as defined by the ESPEN consensus and according to the specific components of the ESPEN definition (independent variables), both adjusted for confounders (n = 179).

	Mortality according to presence of malnutrition, adjusted for confounders					
	Crude analysis			Adjusted analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Malnutrition as defined by the ESPEN consensus	3.1	[1.7 to 5.8]	**0.000**	4.6	[1.7 to 12.0]	**0.002**
Age				1.1	[1.0 to 1.3]	0.089
Gait speed				1.0	[0.1 to 2.5]	0.368
MMSE score				0.9	[0.8 to 1.0]	**0.046**
IADL score				0.6	[0.3 to 1.0]	0.060
Hypertension	1.1	[0.7 to 1.6]	0.712	1.5	[0.9 to 2.7]	0.119
Diabetes mellitus	1.7	[0.6 to 4.6]	0.322	1.3	[0.3 to 5.4]	0.749
Coronary heart disease	2.3	[1.4 to 3.9]	**0.002**	2.7	[1.3 to 5.7]	**0.011**
Components of ESPEN definition	**Mortality according to specific components of the ESPEN definition, adjusted for confounders**					
	Crude analysis			Adjusted analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Unintentional weight loss	1.5	[0.7 to 3.1]	0.259	1.9	[0.8 to 5.0]	0.196
Body mass index	0.6	[0.4 to 0.9]	**0.015**	0.5	[0.3 to 0.8]	**0.003**
Fat-free mass index <15 kg/m^2	0.9	[0.6 to 1.5]	0.802	0.7	[0.3 to 1.3]	0.195
Age				1.1	[1 to 1.3]	**0.049**
Gait speed				0.3	[0.1 to 1.9]	0.203
MMSE score				0.9	[0.8 to 1.0]	0.070
IADL score				0.5	[0.3 to 0.9]	**0.026**
Hypertension	1.1	[0.7 to 1.7]	0.628	2.0	[1.1 to 3.6]	**0.023**
Diabetes mellitus	1.9	[0.7 to 5.4]	0.220	2.0	[0.4 to 8.9]	0.372
Coronary heart disease	2.3	[1.4 to 3.9]	**0.002**	2.6	[1.2 to 5.5]	**0.015**

HR: hazard ratio; CI: Confidence interval; Adjusted analysis: adjustment for age, gait speed at baseline, MMSE at 7-year follow-up, IADL index at 7-year follow-up, hypertension, diabetes mellitus, and coronary heart disease; HR significant (i.e. p < 0.05) indicated in bold.

The use of BMI alone may have limited value to diagnose malnutrition, as obese individuals may exhibit malnutrition, illustrated by lower FFMI [27]. The inclusion of the FFMI in the ESPEN definition is supposed to improve its predictive value by minimizing the effect of sex-based differences in body composition, as women have lower FFMI (and higher fat mass index) than men [5,28]. In addition, the FFMI has been shown to be the most powerful indicator of malnutrition, sarcopenia, frailty, and cachexia in post-acute patients [29]. FFMI is also consistently associated with disease severity among inpatients with chronic obstructive pulmonary diseases [22], and with survival in patients with stable chronic obstructive pulmonary disease and in general population [30]. Unexpectedly, FFMI alone was not associated to long-term mortality in our work; this issue merits further research. FFMI has been highlighted as one of the most important predictors for mortality not just for patients with a diagnosis of malnutrition but also for sarcopenia and cachexia, being the common component in all three definitions [22,31]. A potential explanation of this lack of association in our study might be the limited sample size and limited statistical power, as previously reported when no association was between cognitive decline and body composition [14]. Although FFMI was not a predictor, malnutrition as defined by ESPEN did have prognostic value, as the sum of the parts is stronger than the effect of each separate component [31]; this is an additional strength of the ESPEN definition.

In addition to mortality risk, the ESPEN definition of malnutrition may be of interest in older adults to screen for risk of poor health trajectories. For instance, malnutrition diagnosed with the

ESPEN definition has been associated with worse functional prognosis in older patients during and after post-acute rehabilitation care [29]. In some previous studies, the relationships between ESPEN malnutrition diagnosis and nutrition-related conditions such as frailty, cachexia, and sarcopenia were cross-sectionally established [21,29]. Further longitudinal studies are needed to clarify the clinical prognostic value of the ESPEN diagnosis to predict other adverse clinical outcomes, such as hospital readmissions or falls. In addition, it would be timely to apply the consensus in other community-based cohorts to better understand the relationships between clinical biomarkers, aging, inflammation, and ESPEN malnutrition diagnosis among older adults. Our study highlights the need to apply emerging research findings in clinical settings to improve geriatric care [32].

Some further limitations of the study should be taken into consideration. First, the study cohort was restricted to women and included otherwise healthy participants who may have been more motivated and interested in health issues than the general population of older adults who live in independent senior living environments. Therefore, the studied sample might not be representative of all community-dwelling older adults and our findings should be interpreted with caution. Secondly, due to the *post-hoc* design of the present analysis, most EPIDOS participants could not be included due to lack of information on unintentional weight loss, BMI, FFMI, or vital status; our analysis was limited to the EPIDOS-Toulouse cohort [14], a subsample that provided the information needed to apply the ESPEN criteria. Finally, characteristics of populations change over time. Therefore, the results and conclusions obtained from EPIDOS data may not be transferable to a more recent cohort. In addition, malnutrition might not have the same prognostic impact in the late nineties and in present times; applying ESPEN criteria in a larger, updated cohort could provide additional information about the value of ESPEN criteria to predict clinical outcomes.

Weight loss is clearly the most difficult ESPEN component to obtain, due to poor accuracy in self-reporting among older adults [33], which encourages the systematic measurement of anthropometric variables as part of the comprehensive health assessment of older people [11]. In our study, the availability of data on objective measurement of participants' weight loss, even for a 7-year interval, was a strength of our analysis. Although we were able to control for many characteristics that may have modified the results, residual potential confounders might still be present.

5. Conclusions

Malnutrition, diagnosed by the ESPEN basic definition in 7.3% of this cohort of otherwise healthy community-dwelling French women aged 75 or older, was associated with 4.4-fold increased risk of mortality after 12 years of follow-up. This main result strengthens the long-term prognostic value of the ESPEN definition and encourages clinicians to use this tool in their daily practice in otherwise healthy, community-dwelling, older adults. Further research is needed to better elucidate the possible relationships and interactions between ESPEN malnutrition, inflammation, frailty, and sarcopenia, and to determine their specific impact on long-term life and health trajectories.

Conflict of interest

All authors declare they do not have any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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Author contribution

DSR, EM, XD, and CA wrote the manuscript; DSR, JM, FE, and OV did literature review; AMS, YR, HB, and CA participated in data collection; XD did data analysis; AMS, YR, HB, FE, FE, OV, JM, and CA corrected the manuscript. All co-authors read and approved the final version of the manuscript.

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Investigators of the EPIDOS study. Coordinators: Breart, Dargent-Molina, Meunier, Schott, Hans, and Delmas. Principal investigators: Baudoin and Sebert (Amiens); Chapuy and Schott (Lyon); Favier and Marcelli (Montpellier); Hausherr, Menkes and Cormier (Paris); Grandjean and Ribot (Toulouse).

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