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Unmasking malnutrition through soluble RAGE: A biomarker-guided insight from FRASNET

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ABSTRACT

Background: Malnutrition is a prevalent geriatric syndrome, with multifactorial etiology and consequences for health and independence. Inflammation contributes to nutritional decline, yet conventional inflammatory markers often lack sensitivity for identifying malnutrition risk. The soluble receptor for advanced glycation end-products (sRAGE), a modulator of inflammatory responses, has emerged as a biomarker of disease risk and adverse outcomes in various conditions.

Objectives: to evaluate the association between circulating sRAGE levels and nutritional status in community-dwelling older adults.

Methods: This prospective observational study was conducted within the FRASNET cohort. Fifty-two community-dwelling older adults underwent multidimensional geriatric assessments during two time periods: 2017–2020 and 2023–2024. Serum sRAGE levels were measured at both timepoints. Nutritional status was assessed using the Mini Nutritional Assessment Short Form (MNA-SF). Associations between sRAGE and clinical parameters were evaluated through linear regression models adjusted for age and sex. The diagnostic performance of sRAGE in identifying malnutrition was assessed using ROC curve analysis.

Results: Higher baseline sRAGE levels were significantly associated with lower BMI ($\beta = -0.003$, $p = 0.036$), reduced calf circumference ($\beta = -0.002$, $p = 0.04$), and poorer nutritional status as revealed by MNA-SF scores ($\beta = -0.001$, $p = 0.03$) at follow-up. Associations were more pronounced in women. ROC analysis indicated good diagnostic accuracy for identifying malnutrition risk, with an AUC of 0.85. The optimal sRAGE cut-off value for malnutrition risk was 1362.5 pg/ml.

Conclusions: Higher sRAGE levels were prospectively associated with poorer nutritional outcomes in older adults, particularly in women. sRAGE may aid early identification of inflammation-related malnutrition risk.

1. Background

Malnutrition is a common geriatric syndrome that significantly affects clinical outcomes and undermines functional independence in older adults (Dent et al., 2023). The etiology of malnutrition in later life is complex and typically multifactorial. According to the Global Leadership Initiative on Malnutrition (GLIM) criteria (Cederholm et al., 2019), the causes can be broadly classified into two categories: (i) reduced food intake or impaired nutrient assimilation, and (ii) disease burden and inflammatory conditions. Malnutrition associated with

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inflammation is particularly common in older adults (Schuetz et al., 2021; Dent et al., 2019a). The chronic, low-grade inflammatory state characteristic of aging -referred to as "inflammaging" (Franceschi and Campisi, 2014)-, further increases susceptibility to disease-related nutritional decline in this population. Moreover, chronic inflammation plays a central role in sarcopenia (Cruz-Jentoft and Sayer, 2019), a geriatric condition defined by the progressive loss of muscle function and mass. Sarcopenia and malnutrition often coexist and share overlapping clinical features, though they remain distinct diagnostic entities (Cruz Jentoft et al., 2023).

Biochemical laboratory tests are commonly used to support the identification of malnutrition (Zhang et al., 2017a). However, their utility remains limited by the lack of evidence-based guidelines for their interpretation across different clinical settings and patient populations.

Chronic inflammation and malnutrition interact bidirectionally in older adults: inflammation accelerates muscle wasting, appetite loss, and metabolic imbalance, while malnutrition itself amplifies systemic inflammation, creating a self-perpetuating cycle observed in multiple models of aging. (Franceschi et al., 2018; Hickson, 2006; Dent et al., 2019b; Calder and Jackson, 2000; Morley, 1997; Deutz, 2014; Lesourd, 1997). Diet-associated inflammation has been shown to contribute to muscle decline and sarcopenia in older individuals, supporting the link between nutritional factors, chronic inflammatory burden, and deteriorating nutritional status in aging populations (Balaban et al., 2025).

This self-perpetuating vicious cycle is increasingly recognized as a key biological mechanism underlying inflammation-related malnutrition but is poorly captured by conventional acute-phase reactants, which primarily reflect short-term hepatic responses rather than sustained upstream inflammatory signaling (Ferrucci et al., 2005; Franceschi et al., 2017; Zhang et al., 2017b; Furman et al., 2019; Morlese et al., 1998).

These limitations underscore the need for biomarkers capable of capturing the chronic inflammation-related mechanisms underlying nutritional decline (Ramos-Nino, 2025).

Commonly used acute phase inflammatory markers—such as C-reactive protein (CRP), total lymphocyte count (TLC), and white blood cell (WBC) count—lack the specificity and sensitivity needed to identify malnutrition, particularly in older adults (Zhang et al., 2017a). This limitation underscores the need for biomarkers that better capture the chronic, inflammation-related mechanisms underlying nutritional decline.

The soluble receptor for advanced glycation end-products (sRAGE) pathway represents a biologically plausible link between chronic inflammation, metabolic stress, and malnutrition. It is a circulating isoform of RAGE generated through proteolytic cleavage of the membrane-bound receptor by matrix metalloproteinases (Hanford et al., 2004; Raucci et al., 2008; Barile et al., 2005; Kaji et al., 2007a) or via alternative splicing of the RAGE gene (Yan et al., 2007). sRAGE reflects multiple upstream inflammatory pathways due to its ability to bind a wide range of pro-inflammatory ligands including advanced glycation end-products (AGEs) (Hanford et al., 2004), high-mobility group box 1 (HMGB1) (Schmidt and Stern, 2000), and S100/calgranulin proteins (Hofmann et al., 1999). These ligands are key mediators of chronic inflammation and are implicated in conditions such as chronic kidney disease (Steenbeke et al., 2022), rheumatoid arthritis (Moser et al., 2005), coronary artery disease (Hudson et al., 2005), and aging (Son et al., 2017). Activation of membrane-bound RAGE by its ligands promotes oxidative, stimulates NADPH oxidase activity, enhances the expression of adhesion molecules, and activates NF-κB–dependent inflammatory pathways (Semba et al., 2010; Basta, 2008). Elevated circulating sRAGE levels reflect increased shedding of RAGE in response to heightened inflammatory or metabolic stress (Nakamura et al., 2007; Yilmaz et al., 2011; Diekmann et al., 2021).

However, sRAGE can also acts as a decoy receptor by binding these molecules and preventing their interaction with membrane-bound RAGE. Experimental models show that sRAGE can attenuate AGE–RAGE signaling, thereby reducing inflammation and slowing disease progression in model of diabetes (Bucciarelli et al., 2002; Park et al., 1998; Kaji et al., 2007b). sRAGE may also confer anti-inflammatory effects by functioning as a decoy receptor for HMGB1, a potent pro-inflammatory ligand of RAGE. Notably, HMGB1 has a binding affinity for RAGE approximately ten times higher than that of AGEs (Schmidt and Stern, 2000), although its serum concentrations are lower (Fukami et al., 2009; Takeuchi et al., 2000). These differences in ligand kinetics and abundance suggest that circulating HMGB1, rather than AGEs, may be a more physiologically relevant target of sRAGE under certain conditions (Hanbing et al., 2022; Ruggieri et al., 2024).

This dual biological role suggests that higher sRAGE levels can serve as an integrated marker of chronic inflammatory burden and may indicate vulnerability to inflammation-related nutritional decline (Erusalimsky, 2021).

In humans, evidence of link between sRAGE and malnutrition comes from studies in patients with chronic kidney disease, where sRAGE levels are associated with malnutrition even after adjustment for age and systemic inflammation (Caldiroli et al., 2022), suggesting a role beyond that of conventional inflammatory markers (e.g., CRP). However, the translatability of these findings to other disease condition is uncertain (Maillard-Lefebvre et al., 2009; Santilli et al., 2009; Yamagishi et al., 2007; Geroldi et al., 2003; Brownlee, 2001). Evidence on the association between circulating sRAGE levels and nutritional status in elderly remains inconsistent. Several studies have reported a positive correlation between body mass index (BMI) and sRAGE concentrations (Santilli et al., 2009; Yamagishi et al., 2007), suggesting that higher sRAGE levels may be observed in individuals with greater adiposity. In contrast, other studies have found no significant relationship between BMI and sRAGE (Geroldi et al., 2003; Brownlee, 2001). Adding further complexity, a recent systematic review and meta-analysis reported an inverse association, showing that higher sRAGE concentrations were associated with lower BMI and waist circumference in apparently healthy adults (Tayyib et al., 2023). These discrepancies may be due to differences in study populations and settings. To help clarify this issue, in this prospective observational study we evaluated the role of circulating sRAGE as a predictor of malnutrition focusing on a well-characterized cohort of community-dwelling older adults, thereby minimizing potential confounding across heterogeneous populations and settings.

2. Methods

The study flow diagram is illustrated in Fig. 1. The Frailty and Sarcopenia Network (FRASNET) was a multicenter observational cohort study that enrolled both community-dwelling healthy individuals and institutionalized older adults. The study was approved by the San Raffaele Scientific Institute (approval number: 24/INT/2017), and written informed consent was obtained from all participants prior to inclusion. Recruitment occurred between April 1, 2017, and October 16, 2020. Detailed inclusion and exclusion criteria have been previously reported (Delli Zotti et al., 2022; Damanti et al., 2024a; Damanti et al., 2025; Damanti et al., 2024b). To ensure a homogeneous study population, we excluded institutionalized patients. Between 2023 and 2024, participants were re-contacted by telephone as part of two research initiatives which received independent ethical approval from the Ethics Committee of San Raffaele Hospital: the Age-It project (21/02/2024; approval number CET 88-2024) and PNRR-MAD-2022-12376672 (12/12/2022, approval number CET: 161/INT/2022), a study investigating the molecular underpinnings of sarcopenic obesity. These calls aimed to assess survival status and explore participants' willingness to attend follow-up evaluations. Supported by the National Recovery and Resilience Plan, Age-It is a national research initiative that promotes innovation in aging research and establishes Italy as a central hub in this field. Participants deemed eligible were invited for in-person follow-up visits. In addition to the geriatric assessments previously conducted between 2017 and 2020, the follow-up evaluations offered a detailed appraisal of

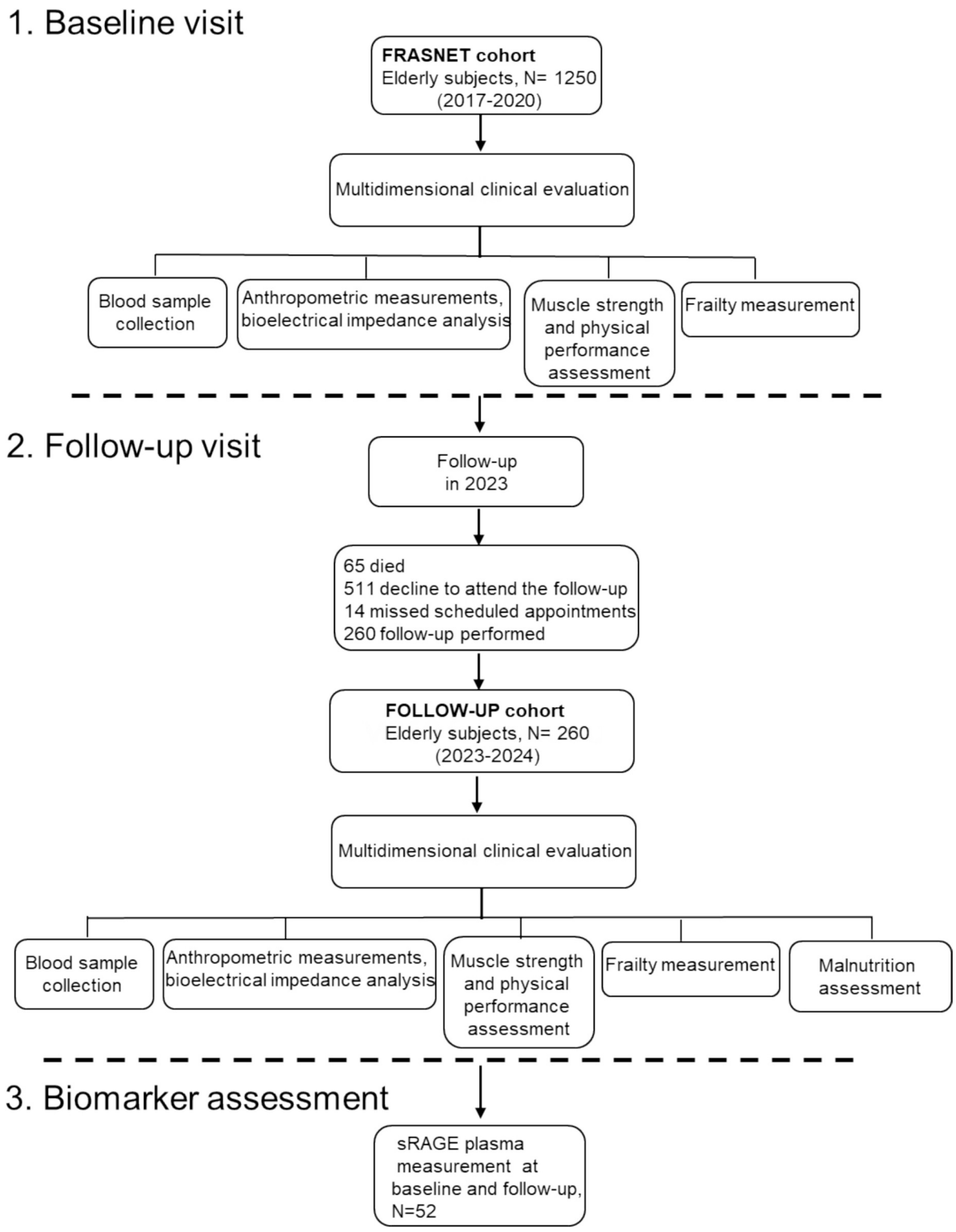

Fig. 1. Study flow diagram.

functional status, including Activities of Daily Living (ADL) and Instrumental ADL (IADL). Fall risk was measured using the Tinetti Scale, while frailty was assessed using the Clinical Frailty Scale (CFS), the Frailty Index (FI), and a modified version of the Frailty Phenotype (FP), in which low BMI replaced unintentional weight loss as a diagnostic criterion. Physical activity was evaluated using the Physical Activity Scale for the Elderly (PASE), balance was assessed via the Tinetti Scale, cognition using the Mini-Mental State Examination (MMSE), and mood through the 15-item Geriatric Depression Scale (GDS-15) while sarcopenia risk was screened using the SARC-F questionnaire. Confirmatory diagnosis of sarcopenia included bioelectrical impedance analysis (BIA) to evaluate muscle mass, and assessments of muscle function through handgrip strength and the Short Physical Performance Battery (SPPB) score. Nutritional status was assessed with the Mini Nutritional Assessment Short Form (MNA-SF). Participants were classified as malnourished when the score was $\leq$7, at risk of malnutrition when scoring 8–11,

and well-nourished with scores of 12–14, in accordance with validated cut-offs (Rubenstein et al., 2001). Comorbidity was assessed using the SNAC-K (Swedish National Study on Aging and Care–Kungsholmen) comorbidity index (Calderón-Larrañaga et al., 2017), which quantifies the burden of chronic diseases based on the presence and severity of multiple conditions commonly observed in older adults. The index provides a cumulative score reflecting overall multimorbidity and has been validated as a robust measure of health status and disease load in geriatric populations.

The selection of prognostic biomarkers relevant to aging, multimorbidity, frailty, and disability was conducted within the Age-It Project through a structured consensus process using the Delphi method. This approach involved iterative rounds of anonymous expert feedback to refine and converge on a final decision. The panel included biologists and clinicians from several Italian universities. Among the candidate biomarkers considered (see Table S1), sRAGE was selected.

Among the 1250 participants initially enrolled in the FRASNET study, as of November 2024, 65 had passed away, 511 declined to attend follow-up visits, 400 did not respond to phone calls, and 46 missed their scheduled follow-up appointments. Ultimately, follow-up visits were successfully conducted for 228 individuals. Within this group, biomarker measurements were performed on samples collected and stored between 2017 and 2020 and during follow up visits performed in 2023–2024 from 52 participants selected based on sample availability (reassessment at follow-up) and financial constraints related to assay costs. These samples were randomly chosen and this subgroup was representative of the overall cohort in terms of demographic and clinical characteristics. Biomarker levels were measured using the ELLA™ automated immunoassay platform (Bio-Techne, San Jose, CA, USA) on blood samples previously collected and biobanked between 2017 and 2020 as part of the FRASNET cohort.

2.1. Statistical analysis

Although the study was exploratory in nature, a post-hoc sensitivity analysis (GPower) indicated that with $n = 52$, $\alpha = 0.05$, and two predictors (age and sex), the study had 80% power to detect an effect size of $f^2 = 0.16$, corresponding to a medium effect according to Cohen's conventions.

Descriptive statistics were employed to summarize the baseline characteristics of the study cohort. For continuous variables, results were reported as means and standard deviations (SD) when data were normally distributed, or as medians with interquartile ranges (IQR) for skewed distributions. Categorical data were expressed as counts (N) and percentages (%). To assess changes in participant characteristics over time, paired *t*-tests were applied to normally distributed continuous variables, while the Wilcoxon signed-rank test was used for non-normally distributed ones. Differences in categorical variables between baseline and follow-up were evaluated using the Chi-squared test.

Comparisons of sRAGE concentrations by sex and by nutritional status (malnourished vs. non-malnourished) were conducted using the Mann–Whitney *U* test. Longitudinal changes in sRAGE levels were assessed with the Wilcoxon signed-rank test. Spearman's rank correlation was used to explore the association between sRAGE concentrations and age. To further explore the associations between sRAGE and key clinical variables—including frailty, malnutrition, muscle mass, physical performance, and functional independence—linear regression models were employed, with all analyses adjusted for age and sex. Analyses were repeated separately for males and females to assess potential sex-specific associations. Regression models were primarily adjusted for age and sex, which are well-established, non-modifiable confounders in studies investigating nutritional status and geriatric syndromes. The inclusion of additional covariates was carefully considered but limited by both methodological considerations and the relatively small sample size ($n = 52$), in order to minimize the risk of model overfitting. BMI was not included in models with MNA-SF as the outcome because it is a component of the nutritional assessment, and its adjustment would have led to over-adjustment and conceptual overlap. Receiver Operating Characteristic (ROC) curve analysis was conducted to identify optimal sRAGE cut-off points for distinguishing between malnourished and well-nourished participants. Cut-offs were determined using the Youden Index, which identifies the point on the ROC curve that maximizes the difference between sensitivity and specificity. The ROC curve provides a visual representation of the balance between sensitivity and 1-specificity across varying thresholds, while the area under the curve (AUC) quantifies diagnostic accuracy. AUC values were interpreted as follows: 0.5 indicates no discriminatory power; values >0.5 to ≤0.7 suggest low accuracy; >0.7 to ≤0.9 indicate moderate accuracy; and >0.9 to <1.0 reflect high diagnostic precision.

3. Results

The biomarker analyses were conducted in a subsample of 52 participants, which represents a modest proportion of the original FRASNET cohort. This sample size was primarily constrained by two feasibility factors: the need for paired serum samples at baseline and follow-up, and financial limitations related to multiplex immunoassay costs. The subsample was randomly selected among participants with complete paired samples and did not differ from the overall cohort in key demographic and clinical characteristics, supporting its representativeness. The subgroup had a median baseline age of 70 years, with women representing 61.5% of participants. Table 1 summarizes the key characteristics of this group, along with the changes observed between the baseline and follow-up assessments. Compared to baseline, follow-up data revealed statistically significant differences in height (from a median of 1.64 m to 1.625 m, $p < 0.001$), in waist circumference (93 cm to 98 cm, $p < 0.001$), in scores on the Fatigue Severity Scale (24 to 33, $p = 0.03$), and in the number of chronic medications used (from 3 to 4, $p < 0.001$).

At follow-up, five subjects were classified as being at risk of

Table 1
Main characteristics of the 52 participants who underwent biomarkers assessment at baseline and during follow-up visits.

	2017–2020	2023–2024	p
Age	70.0 (IQR 68.0–73.0)	76 (IQR 74–78)	<0.001
Females	32 (61.5%)	32 (61.5%)	N.A.
Height (cm)	164 (IQR 1.58–1.71)	162.5 (IQR 157.6–171.0)	<0.001
Weigth (kg)	71.5 (IQR 65.3–77.8)	72.2 (IQR 66.1–77.8)	0.81
BMI (kg/m^2)	26.8 (IQR 24.8–29.7)	26.7 (IQR 25.1–30.2)	0.5
Waist circumference (cm)	93 (IQR 88–101)	98.0 (IQR 89.6–107.0)	<0.001
SPPB total	10 (IQR 9–11)	11 (IQR 9–12)	0.08
FP	1 (IQR 1–1)	0 (IQR 0–1)	0.03
FI	0.10 (IQR 0.05–0.15)	0.13 (IQR 0.05–0.20)	0.22
PASE	105.5 (IQR 70.3–140.3)	109.0 (IQR 83–136.1)	0.88
MMSE	28 (IQR 27–30)	29 (IQR 28–30)	0.03
GDS 15 items	2 (IQR 0–3)	1 (IQR 0–3)	0.06
Fatigue severity scale	24.0 (IQR 17.5–31.0)	33 (IQR 20.25–41)	0.03
Number of long-term use drugs	3 (IQR 1–4)	4 (IQR 3–6)	<0.001

BMI = body mass index; FI = frailty index; FP = frailty phenotype, GDS = geriatric depression scale; MMSE = mini mental state examination; PASE = physical activity scale for the elderly.
Differences over time between continuous variables were assessed using the Wilcoxon signed-rank test whereas differences in categorical variables between baseline and follow-up were evaluated using the Chi-squared test. The significant threshold of p value was set at 0.05.

Table 2
Median levels of biomarkers.

	All (N = 52)	Males (N = 20)	Females (N = 32)	p
2017–2020				
sRAGE (pg/ml)	905.5 (IQR 679.6–1288.0)	806.5 (IQR 642–919)	1094.0 (IQR 751.5–1336.3)	0.02
		Malnourished or at risk of malnutrition (N = 6)	Not malnourished (N = 49)	p 0.30
		1183 (IQR 753–1930.85)	855 (IQR 662–1248)	
2023–2024				
sRAGE (pg/ml)	874.0 (IQR 614.0–1168.0)	675.5 (IQR 568.5–1082.3)	902.0 (IQR 737.0–1171.5)	0.17
		Malnourished or at risk of malnutrition (N = 6)	Not malnourished (N = 43)	p 0.21
		1144.5 (IQR 633.5–1730.5)	838.0 (IQR 581–1050)	

Comparisons of sRAGE concentrations by sex and nutritional status were conducted using the Mann–Whitney U test. Missing data on Mini Nutritional Assessment-short Form for 3 subjects.
The significant threshold of p value was set at 0.05.

malnutrition and one as malnourished, while 43 subjects were not at risk. For three participants, MNA-SF data required to classify nutritional status were not available. Table 2 presents the biomarker levels for the entire sample, as well as stratified by sex and by nutritional status, at both baseline and follow-up. At baseline, sRAGE levels were higher in females than in males and concentrations declined over time. Baseline sRAGE values were higher in subjects who were malnourished or at risk of malnutrition at follow-up visits compared with subjects not at risk. This finding was confirmed by sRAGE measurements performed at follow-up.

Table S2 illustrates the results of the Spearman's rank correlation between sRAGE concentrations and age.

In regression models adjusted for age and sex, baseline sRAGE concentrations were significantly associated with lower calf circumference (B = −0.002, 95% CI: −0.003 to −0.00008, $p = 0.04$), lower body mass index (B = −0.003, 95% CI: −0.005 to −0.0002, $p = 0.036$), and poorer nutritional status as assessed by the MNA-SF (B = −0.001, 95% CI: −0.002 to −0.00009, $p = 0.03$; Table 3) at follow-ups. sRAGE demonstrated moderate diagnostic accuracy for identifying individuals at high risk of malnutrition, with an area under the ROC curve (AUC) of 0.85 (95% C.I. 0.75–0.95) (Fig. 2). The optimal cut-off value, determined using the Youden Index (0.85, sensibility = 1, specificity = 0.146), was 1362.5 pg/ml. When analyses were stratified by sex (Table 4), these associations remained significant in females, specifically for the MNA-SF score ($p = 0.03$).

4. Discussion

4.1. Findings

In this prospective observational study, we found that higher baseline plasma sRAGE concentrations were significantly associated with poorer nutritional status in community-dwelling older adults. Specifically, elevated sRAGE levels predicted lower MNA-SF scores, reduced BMI, and smaller calf circumference during follow-up, supporting the role of this biomarker as a potential indicator of nutritional decline. Importantly, these associations remained robust after adjustment for age and sex and appeared to be particularly pronounced among women, suggesting a possible sex-specific vulnerability in the relationship between sRAGE and nutritional status. Furthermore, although sRAGE concentrations declined over time in the overall cohort, levels consistently remained higher in women compared with men, indicating both a longitudinal trajectory and a persistent sex difference in the biomarker profile.

The stronger association between sRAGE and malnutrition observed in older women may be partly explained by sex-specific differences in body composition and hormonal milieu. Compared with men of similar age, older women generally exhibit higher fat mass and lower lean mass, a pattern that has been associated with increased levels of inflammatory and adipose-related biomarkers (Santoro et al., 2019). Adipose tissue, particularly in the context of age-related redistribution toward visceral depots, is an active source of pro-inflammatory mediators and may contribute to increased production and accumulation of RAGE ligands, including advanced glycation end-products (AGEs), high-mobility group box 1 (HMGB1), and S100 proteins. In addition, post-menopausal hormonal changes, especially declining estrogen levels, are known to influence fat distribution, insulin sensitivity, oxidative stress, and inflammatory signaling pathways. Sex hormones have been shown to be differentially associated with metabolic parameters and body composition in men and women, with estrogen deficiency promoting a pro-inflammatory and metabolically unfavorable profile (Ciardullo et al., 2023). These hormonal and metabolic alterations may further amplify RAGE pathway activation and ligand availability in older women. Collectively, these sex-specific biological factors may result in a higher chronic inflammatory burden in women, which sRAGE is particularly well suited to capture due to its ability to integrate signals from multiple upstream inflammatory ligands. This may explain why sRAGE appears to be a more sensitive biomarker of inflammation-related nutritional vulnerability in older women than in men, and highlights the importance of considering sex as a relevant biological modifier in studies of aging, inflammation, and malnutrition.

Table 3
Associations between biomarkers dosed on 2017-2020 samples and various parameters of the multidimensional evaluations conducted during follow-up visits in 2023-2024

	Univariable				Multivariable		
	B	95% C.I.	p		B	95% C.I.	p
Calf circumference							
sRAGE	−0.002	−0.004 to −0.001	0.01	sRAGE	−0.002	−0.003 to −0.00008	0.04
Visceral fat							
sRAGE	−0.002	−0.005 to −0.0002	0.04	sRAGE	−0.002	−0.004–0.001	0.14
BMI							
sRAGE	−0.003	−0.005 to −0.0002	0.031	sRAGE	−0.003	−0.005 to −0.0002	0.036
Weight							
sRAGE	−0.008	−0.016 to −0.0004	0.04	sRAGE	−0.006	−0.014–0.002	0.14
MNA – SF							
sRAGE	−0.001	−0.002 to −0.0002	0.03	sRAGE	−0.001	−0.002 to −0.00009	0.03

BMI = body mass index; MMA-SF = Mini Nutritional Assessment Short Form.
Linear regression analyses. Multivariable models adjusted for age and sex. The significant threshold of p value was set at 0.05.

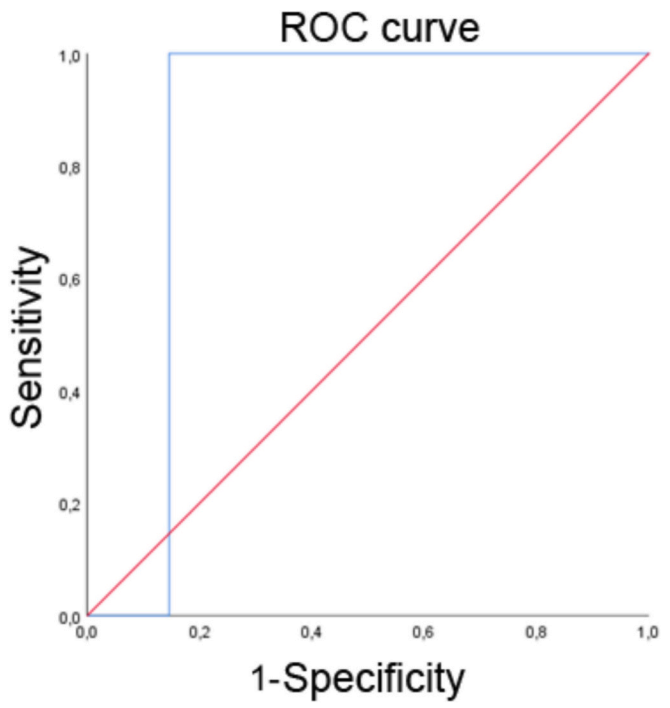

Fig. 2. Receiver operating characteristic (ROC) curve for sRAGE in predicting malnutrition. The area under the curve (AUC) is 0.85 (95% CI: 0.75–0.95). The optimal cut-off identified (1362.5 pg/ml) corresponds to a sensitivity of 1.00, specificity of 0.146, and a Youden Index of 0.85.

4.2. Novelty

To our knowledge, this is the first study to demonstrate a prospective association between circulating sRAGE concentrations and nutritional decline in community-dwelling older adults. Previous reports have largely focused on hospitalized or diseased populations, such as patients with chronic kidney disease (Caldiroli et al., 2022), whereas our results extend this evidence to a healthier, community-based cohort. By adopting validated and widely used clinical measures -including the Mini Nutritional Assessment Short Form and calf circumference- we provide a robust and clinically meaningful evaluation of nutritional status, which enhances the translational relevance of our findings. Another novel aspect is the observation of sex-specific effects: associations between higher sRAGE levels and poorer nutritional outcomes were more pronounced in women, a result that contributes to the growing body of evidence suggesting that sRAGE biology may be modulated by sex. This finding not only enriches the interpretation of our data but also opens new avenues for exploring sex-related mechanisms in the relationship between inflammation, sRAGE, and nutritional vulnerability in aging.

4.3. Interpretation

Our findings suggest that sRAGE may serve as a biomarker of vulnerability to inflammation-driven malnutrition in older adults. The consistent associations we observed between higher baseline sRAGE levels, lower BMI, and poorer nutritional status as assessed by the MNA-SF point toward a biologically plausible link between this circulating receptor and nutritional decline. This concordance across different measures of undernutrition reinforces the robustness of our results and supports the view that sRAGE reflects systemic vulnerability relevant to aging.

A possible explanation lies in the dual and context-dependent role of sRAGE. On the one hand, circulating sRAGE may act as a decoy receptor, binding ligands such as AGEs and HMGB1 and thereby preventing activation of membrane-bound RAGE and downstream inflammatory cascades. On the other hand, elevated plasma concentrations may also reflect increased tissue expression and subsequent shedding of RAGE under conditions of chronic inflammation or metabolic stress. In this latter scenario, higher sRAGE levels would not necessarily indicate protection, but rather a compensatory mechanism in response to sustained inflammatory activation.

In our cohort, the negative association of sRAGE with both BMI and MNA-SF strengthens the interpretation that increased circulating sRAGE is a marker of heightened inflammatory vulnerability rather than a benign signal. Taken together, these observations support the hypothesis that sRAGE integrates complex inflammatory and metabolic signals, and may represent an early indicator of nutritional risk in older individuals.

4.4. Comparison to prior literature

Our results are consistent with previous evidence from clinical populations, such as patients with chronic kidney disease, where higher circulating sRAGE concentrations have been reported in malnourished individuals (Caldiroli et al., 2022). These findings support the notion that sRAGE may reflect nutritional vulnerability in settings characterized by systemic inflammation and metabolic stress. At the same time, our data partially diverge from studies that have investigated weight-based definitions of malnutrition or obesity-related outcomes (Maillard-Lefebvre et al., 2009; Santilli et al., 2009; Yamagishi et al., 2007). Some reports have suggested a positive association between BMI and sRAGE (Kaji et al., 2007b; Fukami et al., 2009; Takeuchi et al., 2000), implying that greater adiposity may be linked to higher circulating levels of the receptor. In contrast, the present study found that higher sRAGE concentrations were associated with lower BMI and lower MNA-SF scores, in line with a recent meta-analysis (Tayyib et al., 2023) that demonstrated an inverse relationship between sRAGE, BMI, and waist circumference in apparently healthy adults. These discrepancies likely reflect differences in study populations (community-dwelling versus diseased or hospitalized cohorts), the criteria used to define malnutrition, the extent of underlying inflammatory activation, and technical variations in the measurement of sRAGE. Collectively, these contextual factors highlight the complexity of interpreting sRAGE biology across different clinical and demographic settings and underscore the need for standardized approaches in future investigations.

4.5. Limitations

This study has some limitations that should be acknowledged. First, the relatively small size of the biomarker subcohort limits the statistical power of our analyses and may reduce the generalizability of the findings, particularly for subgroup comparisons by sex. Although the longitudinal design provides strength in demonstrating predictive associations, the modest sample size means that our results should be considered preliminary and require confirmation in larger cohorts. In addition, the relatively small sample size limited the number of covariates that could be included in multivariable models without increasing the risk of overfitting. Although age and sex were included as core confounders, and sensitivity analyses accounting for comorbidities and polypharmacy supported the robustness of the main findings, residual confounding cannot be fully excluded. In particular unmeasured or insufficiently powered factors related to the multifactorial etiology of malnutrition may have influenced the observed associations. Second, we did not assess the full panel of RAGE ligands, such as AGEs or HMGB1, which play a central role in the activation of the RAGE pathway. The absence of these measures prevents a more detailed exploration of the mechanistic underpinnings of the observed associations and makes it difficult to determine whether elevated sRAGE levels reflect protective decoy activity or a compensatory response to chronic ligand stimulation. Finally, given the observational nature of the study, causality cannot be inferred. Our findings should therefore be interpreted as evidence of

Table 4
Associations between biomarkers dosed on 2017-2020 samples and various parameters of the multidimensional evaluations conducted during follow-up visits in 2023-2024 in females and males

	Univariable				Multivariable		
	B	95% C.I.	p		B	95% C.I.	p
Females							
Calf circumference							
sRAGE	−0.002	−0.004 to −0.0001	0.01	sRAGE	−0.001	−0.003 to −0.0004	0.12
Visceral fat							
sRAGE	−0.002	−0.004 to −0.0001	0.04	sRAGE	−0.001	−0.003–0.001	0.20
BMI							
sRAGE	−0.003	−0.006 to −0.00001	0.05	sRAGE	−0.05	−0.005 to −0.001	0.2
Weight							
sRAGE	−0.007	−0.016 to −0.002	0.04	sRAGE	−0.004	−0.013–0.005	0.38
MNA – SF							
sRAGE	−0.001	−0.002 to −0.00002	0.055	sRAGE	−0.001	−0.002 to −0.0001	0.03
Males							
Calf circumference							
sRAGE	−0.001	−0.005–0.003	0.01	sRAGE	−0.001	−0.005–0.003	0.61
Visceral fat							
sRAGE	−0.002	−0.006–0.006	0.94	sRAGE	−0.001	−0.008–0.006	0.75
BMI							
sRAGE	−0.001	−0.005–0.004	0.67	sRAGE	−0.002	−0.007–0.003	0.46
Weight							
sRAGE	−0.0005	−0.018–0.017	0.04	sRAGE	−0.005	−0.022–0.013	0.59
MNA – SF							
sRAGE	0.0001	−0.001–0.001	0.86	sRAGE	0.0001	−0.001–0.001	0.82

BMI = body mass index; MMA-SF = Mini Nutritional Assessment Short Form.
Linear regression analyses. Multivariable models adjusted for age and sex. The significant threshold of p value was set at 0.05.

association rather than proof of a direct causal link between sRAGE concentrations and nutritional decline. Future studies with larger sample sizes will be necessary to confirm these results and to enable more comprehensive multivariable adjustment, thereby improving causal inference.

5. Conclusions

From a clinical perspective, our findings suggest that sRAGE could serve as a valuable biomarker for the early identification of older adults at risk of malnutrition. While we did not directly compare conventional inflammatory markers such as CRP with sRAGE, it reflects multiple pro-inflammatory ligands involved in chronic inflammation and may have a superior diagnostic performance to identify malnutrition risk. Incorporating sRAGE into geriatric assessments could therefore improve risk stratification and enable earlier, targeted interventions.

At the same time, further research is needed to validate these preliminary results. Larger and more diverse cohorts are required to confirm the predictive value of sRAGE across different populations and clinical settings. In addition, mechanistic studies that include simultaneous measurement of RAGE ligands such as AGEs and HMGB1 will be essential to clarify the biological pathways underlying the observed associations. These future investigations will help determine whether sRAGE is merely a biomarker of nutritional risk or whether it could also become a target for interventions aimed at mitigating inflammation-related malnutrition in aging.

CRediT authorship contribution statement

Sarah Damanti: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Clara Sciorati:** Writing – original draft, Investigation, Formal analysis, Data curation. **Amanda Avola:** Investigation, Data curation. **Rebecca De Lorenzo:** Investigation, Formal analysis. **Maria Pia Ruggiero:** Data curation. **Simona Santoro:** Data curation. **Eleonora Senini:** Data curation. **Marco Messina:** Data curation. **Francesca Farina:** Data curation. **Costanza Festorazzi:** Data curation. **Giulia Pata:** Data curation. **Martina Laffranchi:** Investigation. **Martina Mallus:** Investigation. **Elena Brioni:** Investigation. **Lorena Citterio:** Formal analysis. **Laura Zagato:** Investigation. **Marco Simonini:** Data curation. **Chiara Lanzani:** Data curation, Conceptualization. **Paolo Manunta:** Supervision, Conceptualization. **Angelo Manfredi:** Supervision. **Patrizia Rovere-Querini:** Supervision, Resources, Conceptualization.

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Declaration of competing interest

The authors declare non-financial interests that are directly or indirectly related to the work submitted for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2026.113032.

Data availability

Data will be made available on request.

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