



Nutritional status and functionality in geriatric rehabilitation patients: a systematic review and meta-analysis

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Key summary points

Aim This systematic review and meta-analysis aims to characterize the nutritional status of geriatric rehabilitation patients and its association with functional parameters.

Findings Malnutrition is prevalent in a relevant percentage of geriatric rehabilitation patients, whereas body mass index (BMI) is in the normal to overweight range. Furthermore, data suggest that protein and energy intake is reduced and vitamin D deficiency is prevalent in this population. Decreased physical function is associated with malnutrition according to Mini-Nutritional Assessment (MNA) and MNA short form, whereas BMI did not show any clear association.

Message Nutritional status is reduced in a relevant percentage of geriatric rehabilitation patients and associated with decreased physical function which emphasizes the need for screening and targeted interventions.

Abstract

Purpose Since there is only limited evidence available for geriatric rehabilitation patients, this systematic review and meta-analysis aims to characterize the nutritional status in this population and its relationship with functionality.

Methods Eight databases were searched for full-text articles reporting baseline nutritional intake and status of adults ≥ 60 years in rehabilitation settings. Pooled estimates were calculated for prevalence of malnutrition and risk of malnutrition based on the Mini Nutritional Assessment (MNA) and for mean body mass index (BMI). Associations between nutritional status (MNA, MNA short form and BMI) and functional status (Barthel Index and Functional Independence Measure) and prevalence of sarcopenia were reviewed.

Results 62 out of 1717 references were eligible for inclusion. Pooled prevalence [95% confidence interval (CI)] of malnutrition and risk of malnutrition were 13 (5–20) % and 47 (40–54) %. Pooled estimate (95% CI) for BMI was 23.8 (23.2–24.5) kg/m². Existing data suggest a risk for low protein and energy intake and vitamin D deficiency. Functional status differed widely. Seven out of ten studies reported significant associations between reduced nutritional status and reduced functionality, whilst two out of seven studies reported significant associations between higher BMI and functionality. Prevalence of sarcopenia was high with 40–76% in this population.

Conclusions Although geriatric rehabilitation populations and settings were heterogeneous, a relevant percentage of geriatric rehabilitation patients were affected by a reduced nutritional status. Nutritional status was associated with decreased functionality. This emphasizes the need for screening for malnutrition and targeted nutritional intervention.

Keywords Geriatric rehabilitation · Nutritional status · MNA · BMI · Meta-analysis · Systematic review

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Introduction

Recent studies in older patients have illustrated the relevance of nutritional status for recovery from acute illness and functional capacity [1]. Good nutritional status allows for faster recovery from illness, shorter hospital stays and reduced rates of readmission [2]. Malnutrition and weight loss, body mass index (BMI) values lower than 20 kg/m², reduced food intake in general and reduced protein intake specifically are established independent factors which negatively influence functional parameters in older people [3, 4]. While nutritional status and its association with functionality has been well examined in community-dwelling older individuals [5–7], in older hospital patients [2, 8] and in nursing home residents [9, 10], only scarce information is available in geriatric rehabilitation. The majority of patients in a geriatric rehabilitation setting is significantly older than 70 years, multimorbid and has a reduced functional status, which necessitates nursing care for activities of daily living [11]. In addition, the nutrition-related diseases sarcopenia and frailty [12] are highly prevalent in this population [13, 14]. The goal of geriatric rehabilitation is to stimulate functional recovery and thereby allow patients to return to their homes [11, 15, 16].

In general, geriatric rehabilitation consists of a structured program, which is in most countries provided by a team of physicians, nurses, physiotherapists, occupational therapists, speech therapists, psychologists, dietitians and social workers [17]. The meta-analysis of Bachmann et al. showed effectiveness of inpatient rehabilitation in older patients (≥ 55 years) in a multidisciplinary rehabilitation setting with regard to the recovery of physical function [15]. However, data describing the nutritional status in detail beyond a questionnaire-based diagnosis of malnutrition are very limited in this population. Geriatric rehabilitation patients, such as hip fracture or heart failure patients are in most cases transferred from acute hospital wards and especially these patient groups have a high prevalence of malnutrition [18–20]. Profound insight into the nutritional situation of geriatric rehabilitation patients appears to be warranted, as specific nutritional interventions might help to stimulate the restoration of functional capacity in this highly vulnerable population.

The aim of the present systematic literature review and meta-analysis was to describe the nutritional status of the geriatric rehabilitation population in detail and to investigate the interrelationship between nutritional and functional outcomes.

Materials and methods

This systematic literature review was performed following the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines [21, 22].

Search strategy

The literature database search was carried out in November 2016, including the following databases: Cab Abstracts, MEDLINE, EMBASE, Current Contents, Allied & Complementary Medicine, British Nursing Index, Global Health, and PsycINFO. The search was not restricted by publication year or language. Additional references were identified by screening reference lists of narrative or systematic reviews retrieved from database search. The search string consisted of keywords describing older people, rehabilitation, nutritional status and functionality. The full search terms are shown in Online Resource 1. A search update was performed in June 2018.

Selection of studies

After removing duplicates, titles and abstracts of all records retrieved by the search process were screened independently for eligibility by two researchers (JvW and JW). The eligible groups were compared, and inconsistencies were discussed and resolved. In a second selection step, the full texts of all eligible records were screened for predefined inclusion and exclusion criteria by three researchers (CvdB, JvW and JW). A random cross-check (43%) was done by a second reviewer, and discrepancies were discussed until resolved. Only full-text articles were considered.

Study population

Studies investigating a population of older adults, aged 60 years and older attending inpatient or outpatient geriatric rehabilitation, were eligible for inclusion. Geriatric rehabilitation was defined to take place in sub-acute rehabilitation facilities for a wide range of medical conditions such as hip fracture, hip replacement, cardiac, pulmonary, stroke rehabilitation and others. Studies with participants in residential aged care facilities, in mental health facilities or drug and alcohol rehabilitation centers, in palliative care settings and studies recruiting solely cognitively impaired participants or exclusively those with dysphagia requiring a texture-modified diet were excluded.

Nutritional and functional parameters

References were included if they reported on nutritional status parameters on admission to rehabilitation care. Eligible nutritional status parameters were not defined up front, because comparability of parameters had the highest priority. Articles were included if baseline nutritional data were present including information on malnutrition and risk of malnutrition based on established screening tools [e.g., Mini Nutritional Assessment (MNA), MNA short form (MNA-SF) and Malnutrition Universal Screening Tool (MUST)], anthropometric parameters (e.g., BMI, body circumferences and skinfold measurements), body composition parameters (e.g., fat mass, fat-free mass, muscle mass), nutrition-related blood marker (e.g., albumin, micronutrient status) as well as nutritional intake parameter (e.g., energy and protein intake). Sarcopenia status, frailty status, muscle strength parameters, parameters reflecting muscle function (e.g., mobility, gait and balance tests) and functional status parameters [e.g., Activities of Daily Living (ADL) and instrumental ADL (IADL)] were extracted if available.

Type of studies

Studies were eligible for inclusion if they were observational studies including cohort, case–control and cross-sectional studies as well as comparative studies with concurrent and non-concurrent controls. Studies with a qualitative study design and case report studies were excluded. Furthermore, studies published in languages other than English, Dutch or German were excluded for practical reasons.

Data extraction

Data extraction was performed by the three researchers (CvdB, JvW, JW). Data extraction included geriatric rehabilitation patient characteristics, description of the rehabilitation setting, and baseline nutritional and functional outcomes, measured at admission to rehabilitation. Values were extracted as values for total groups when available. If an overall value of the total group was not provided in the study publication, data of subgroups were converted into a calculated weighted average for the total group. Extracted data were cross-checked in 37% of the cases to increase the quality of data extraction. Discrepancies were resolved by discussion.

Statistical analysis

For the meta-analysis, data were pooled for MNA, BMI and albumin using the `rma.uni` function of `metafor` package [23] in R (R Foundation for Statistical Computing, Vienna, Austria) [24]. For BMI and albumin, mean values were pooled.

For MNA, the percentage of subjects with malnutrition and subjects at risk of malnutrition were pooled. When the standard deviations were missing, imputation based on available publications was performed by calculating the weighted average variance of similar studies as recommended in the Cochrane Handbook (section 16.1.3.1) [25].

Due to heterogeneity among studies, a random-effects model was fitted with mean as outcome using restricted maximum likelihood estimation (REML) in `metafor` package (version 1.9-9) in R [Version 3.3.3 (2017-03-06)] software to acquire a pooled mean estimate. As the number of studies is adequate, normal distribution was used to obtain a 95% confidence interval (CI) for the overall effect [23].

Quality assessment

Quality assessment was carried out according to the quality assessment tool for observational and cross-sectional studies of the National Heart, Lung and Blood Institute (NHLBI) [26] by two researchers (CvdB, JW) and reviewed by the other researcher (Online Resource 14).

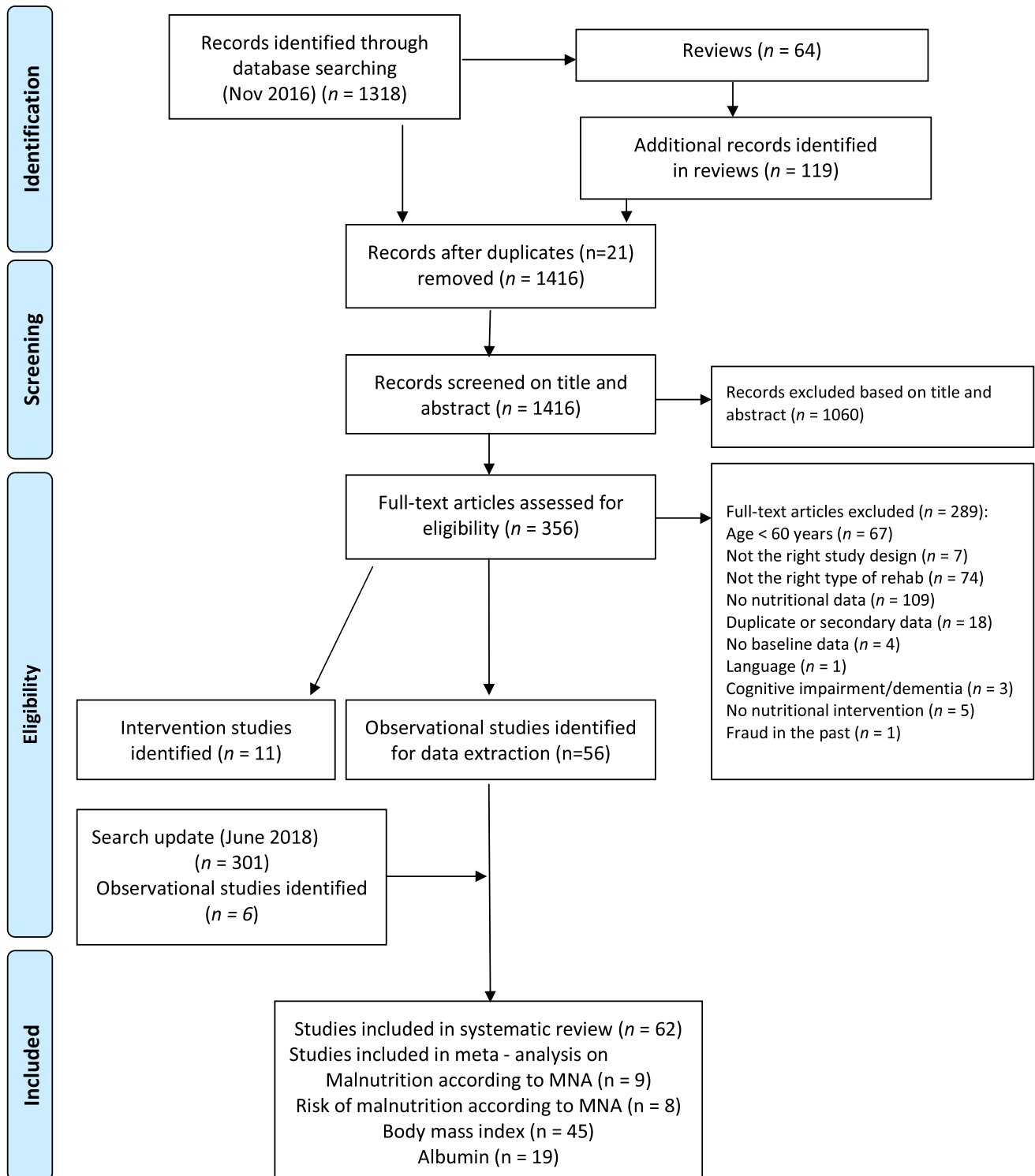
Results

Search results

In total, we identified 1416 references, of which 62 papers fulfilled inclusion criteria for this systematic review (Fig. 1). Three hundred and one references were assessed during a search update.

Description of the geriatric rehabilitation population

The 62 papers included a total of 19,127 geriatric rehabilitation patients from 4 continents. The majority of studies were conducted in Europe ($n=26$) followed by Asia ($n=19$), Australia/New Zealand ($n=13$), North America ($n=3$) and South America ($n=1$) [27]. Study size varied between 20 [27, 28] and 2650 [29] participants. The mean age of the geriatric rehabilitation study population ranged between 72 [30] and 85.4 [31, 32] years. Some studies focused on rehabilitation for a specific main diagnosis, such as hip fracture ($n=12$), cardiac disease ($n=4$), pulmonary disease ($n=3$) or stroke ($n=4$). However, most studies ($n=26$) included more heterogeneous study populations with a wide array of diagnoses, most of which are highly prevalent in old age. Additionally, 13 studies did not provide the leading disease diagnosis. The length of stay in geriatric rehabilitation ranged between 10 [33] and 173 days (subgroup in Nishioka [34]). In only four studies, the mean length of stay was ≥ 60 days [31, 34–36] (Online Resource 2). Not all



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Fig. 1 Flow chart of screening and selection studies

nutritional measurements reported in the included articles could be included in the present review, but they are listed in Online Resource 2.

Nutritional status

Prevalence of malnutrition

Malnutrition and risk of malnutrition were assessed by a variety of commonly used and also by some less established tools. Prevalence of malnutrition ($n=9$) and risk of malnutrition ($n=8$) according to the MNA (0–16 points and 17–23.5 points, respectively) were most often reported. Values ranged between 3% [37] and 33% [38] for malnutrition and between 28% [39] and 58% [30] for risk of malnutrition. A pooled estimate (95% CI) indicated that on average 13 (5–20) % of geriatric rehabilitation patients were malnourished [30, 33, 37–43] and 47 (40–54) % were at risk of malnutrition [30, 33, 37–39, 41–43] according to the MNA (Figs. 2, 3). Prevalence of malnutrition and risk of malnutrition according to other screening tools ($n=19$) ranged between 6% [37] and 88% [44] (Online Resource 3).

Body mass index (BMI)

A pooled estimate per continent [27, 28, 30–33, 35–39, 41–74] showed the lowest mean (95% CI) BMI in Eastern Asia with 21.1 (20.3–21.9) kg/m^2 ($n=13$) followed by Europe 24.6 (23.9–25.2) kg/m^2 ($n=16$) and Australia 25.6 (24.8–26.3) kg/m^2 ($n=10$) (Fig. 4). Prevalence of underweight according to the WHO standards (<18.5 or 19 kg/m^2) ranged between 0% [51] and 17% [61]. According to age-specific cutoff points, reflecting current expert opinions, prevalence of underweight ($<20 \text{ kg/m}^2$) was 21% [28]. No study reported the prevalence of obesity ($\geq 30 \text{ kg/m}^2$) (Table 1).

Biochemical nutritional status markers

Albumin was the most frequently reported blood marker that was presented in 25 studies. Mean (95% CI) pooled estimate of albumin was 34.1 (32.9–35.4) g/L [28, 32, 35–37, 40–42, 45–47, 50, 52–54, 56, 58, 59, 66, 69, 75, 76] (Online Resource 4). Prevalence of reduced albumin levels ($n=5$) ranged between 10.4% ($\leq 30 \text{ g/L}$) [77] and 100% ($< 37 \text{ g/L}$) [56]. Prevalence of vitamin D deficiency according to

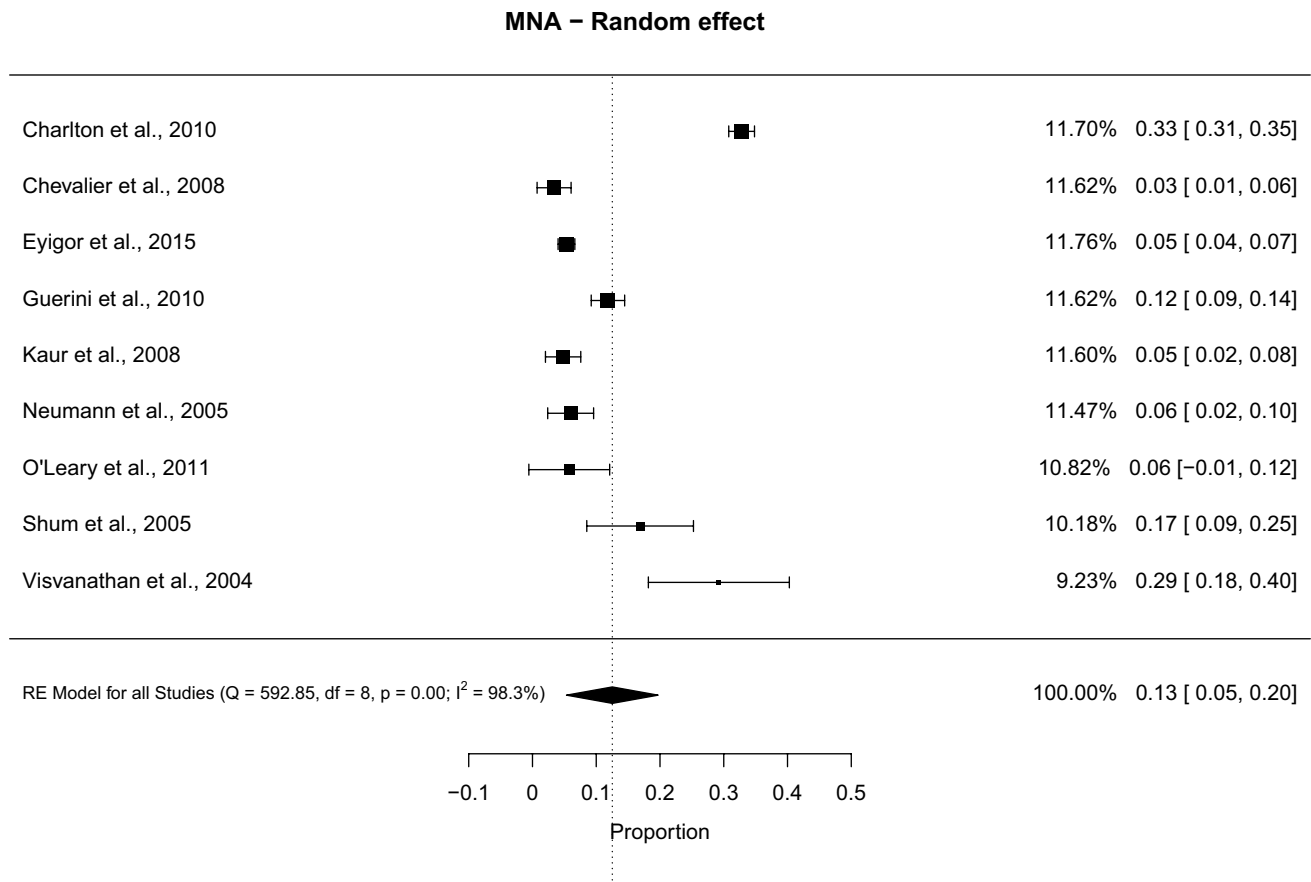


Fig. 2 Pooled prevalence of malnutrition in geriatric rehabilitation patients according to Mini Nutritional Assessment in a random-effects model

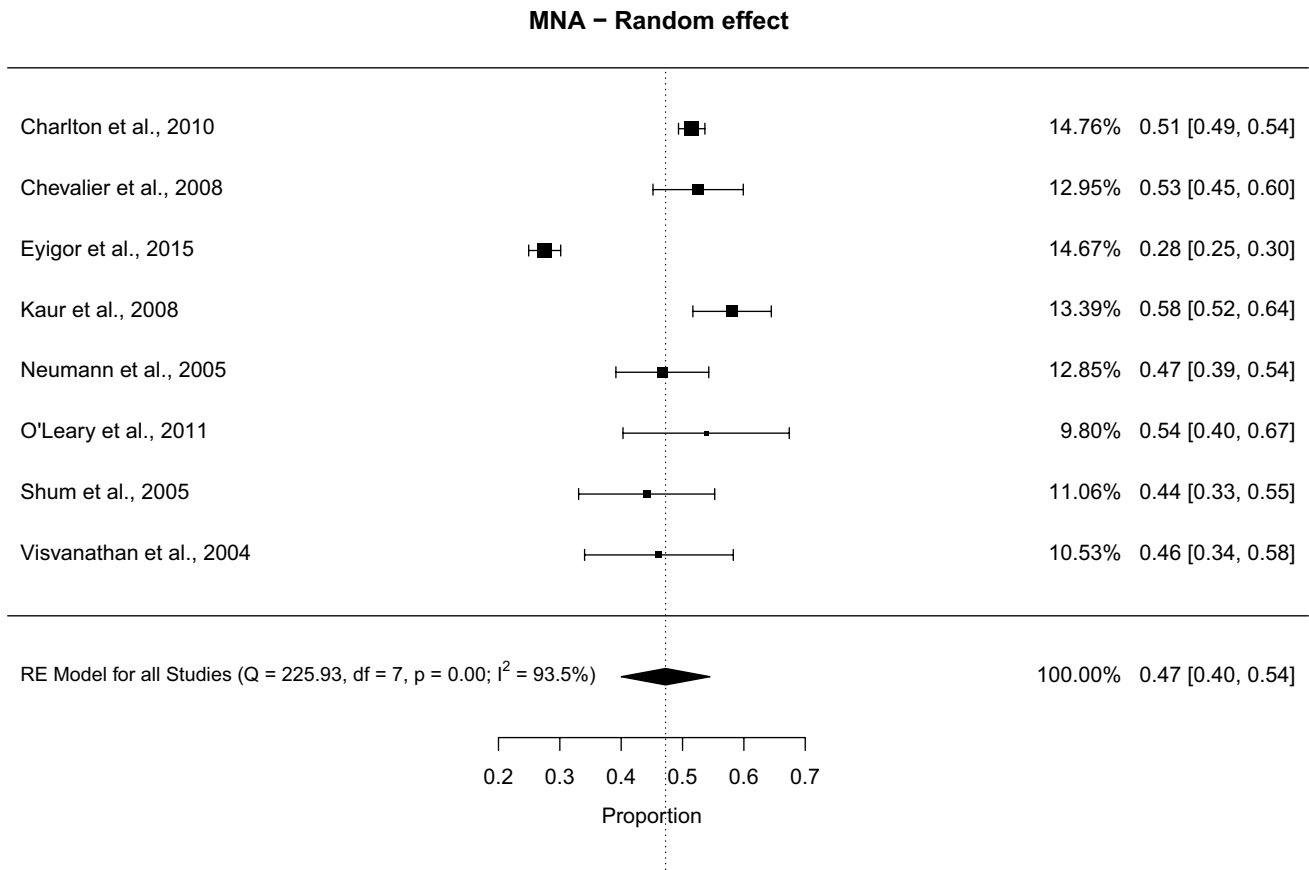


Fig. 3 Pooled prevalence of risk of malnutrition in geriatric rehabilitation patients according to Mini Nutritional Assessment in a random-effects model

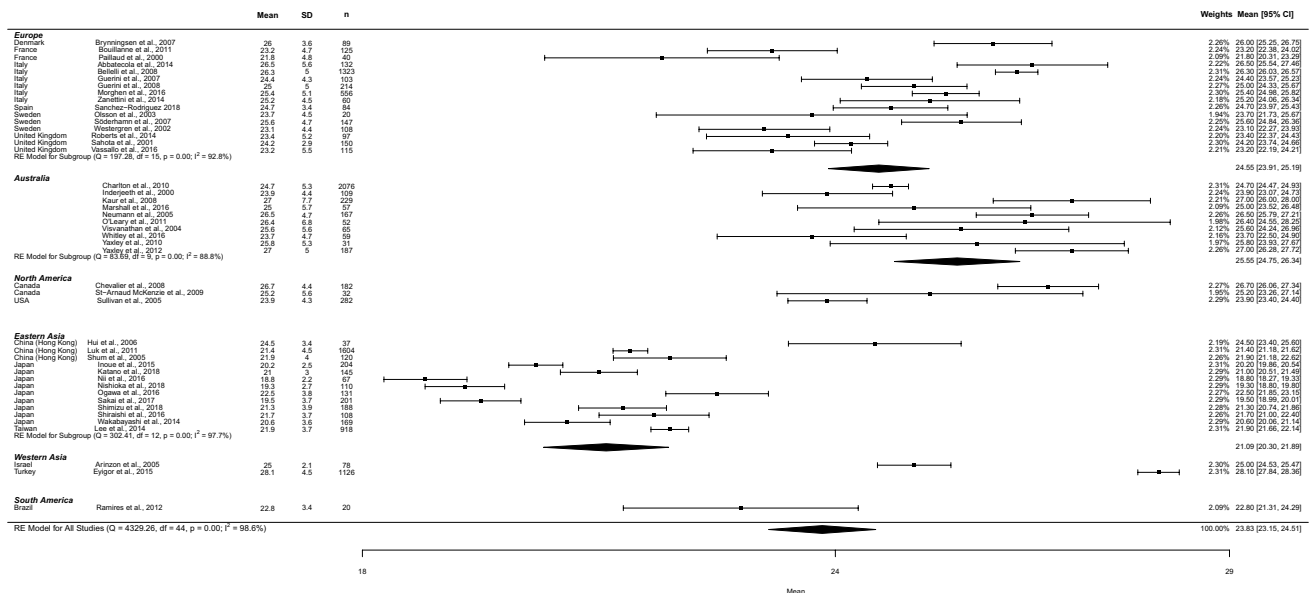


Fig. 4 Pooled average of body mass index (kg/m²) of geriatric rehabilitation patients by continents in a random-effects model

Table 1 Prevalence of low, normal and high BMI groups according to different cut off levels in geriatric rehabilitation patients divided by country

Country	Author, year (n)	Low BMI		Normal BMI		High BMI	
		Cut off (kg/m ²)	%	Cut off (kg/m ²)	%	Cut off (kg/m ²)	%
Western countries							
Australia	Bacon et al. (1995) (n = 369) [96]	< 22	47	22 to < 27	40	> 27	13
Australia	Comans et al. (2011) (n = 107) [79]	< 24	39	24 to < 29	30	> 29	31
Australia	Marshall et al. (2016) (n = 57) [44]	< 22	30	22 to < 27	40	> 27	30
Australia	Neumann et al. (2005) (n = 133) [33]	< 22	17	≥ 22	83	–	–
Australia	Yaxley et al. (2010) (n = 31) [72]	< 22	26	22 to 27	39	> 27	36
Canada	Chevalier et al. (2008) (n = 182) [37]	< 22	15	22 to 24	16	–	–
Spain	Sánchez-Rodríguez et al. (2018) (n = 84) [32]	< 18.5	4.8	–	–	–	–
Sweden	Olsson et al. (2003) (n = 20) [28]	< 20	21	< 24	47	–	–
Sweden	Söderhamn et al. (2007) (n = 31) [65]	–	–	< 24	41	–	–
United Kingdom	Sahota et al. (2001) (n = 150) [61]	< 19	17	–	–	–	–
Non-Western countries							
Brazil	Ramires et al. (2012) (n = 20) [27]	< 18.5	15	18.5 to < 25	60	≥ 25.0	25
China	Hui et al. (2006) (n = 37) [51]	< 18.5	0	18.5 to 24	38	> 24	62

BMI body mass index

established cut off values (<25 nmol/L or <50 nmol/L) was not reported, but one study reported a prevalence of reduced vitamin D (<28 nmol/L) in 67% [52] (Online Resource 5). Micronutrient blood levels are shown in Online Resource 6.

Nutritional intake

Energy intake varied between 1260.4 ± 387.8 [63] and 2048 ± 524 kcal [41] [mean \pm standard deviation (SD)] and 22.8 (9.0) [54] and 33.2 (10.6) kcal/kg body weight (bw) per day [36] [median interquartile range (IQR)]. Protein intake (mean \pm SD) ranged from 43.5 ± 13.7 [63] to 88 ± 21 g per day [41] and was 0.98 ± 0.27 g/kg body weight per day in the only study [66] that reported protein intake related to body weight. There was no information available on the prevalence of low energy or protein intake that would have reflected any available cut offs for these two parameters. Data on energy and macronutrient intake are shown in Online Resource 7, micronutrients intakes are shown in Online Resource 6.

Muscle strength and function

Handgrip strength was most commonly measured and values ranged between 11.8 ± 6.7 [53] and 26.3 ± 6.5 [58] kg (mean \pm SD). Although this parameter is gender specific, only one study differentiated between men and women. There were no data available that reported the prevalence of reduced handgrip strength. An overview of handgrip strength values and other strength measurements is presented in Online Resource 8.

Muscle function was assessed in 17 studies (Online Resource 9). A high risk of falls according to Tinetti (<19 points) was prevalent in 62% [29] of geriatric rehabilitation patients and according to the Physical Performance Test (<8 points) in 28% [78]. Balance problems according to the Romberg scale were prevalent in 42% [79] of the patients.

Functional status

In total, 39 studies reported on ADL or IADL (Online Resource 10). The most commonly applied tool was the Barthel Index (BI). BI scores ranged between 19.8 ± 0.3 and 92 ± 7.7 points (mean \pm SD). Most studies reported a BI between 42.4 ± 21.6 and 65.5 ± 26.3 points (mean \pm SD) representing a reduced functional status (Online Resource 10). The total Functional Independence Measure (FIM) score had a broad range between 56 (43.5) [36] and 88.5 (41.0) points [63] (median (IQR)). The Katz ADL score and the Lawton Brody IADL score ranged from 2.6 ± 1.9 [78, 80] to 3.9 ± 1.9 points [35] and from 1.7 ± 1.8 [55] to 4.8 ± 2.6 points [80]

(mean \pm SD), respectively, indicating reduced status of ADL and IADL.

Body composition, sarcopenia and frailty

Body composition was measured in ten studies with bio-electrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DEXA) (Online Resource 11). Only five of ten studies represented gender-specific data on body composition. The prevalence of reduced muscle mass was described only by one study which reported a reduced SMMI (women <5.4 kg/m², men <7.0 kg/m²) in 42.3% of women and 57.7% of men [63]. The prevalence of sarcopenia was reported in two studies and was 76.1% [62] according to the consensus definition of the Asian working group for sarcopenia and 40% (34% men, 46% women) [73] according to reduced fat-free mass index and quadriceps strength. Prevalence of frailty according to Fried was reported in one study [39]; 14.8% were frail and 55.6% prefrail.

Association between nutritional status and functional status

The association between nutritional status (MNA or MNA-SF) and functional parameters (BI or FIM) was analyzed in ten studies (Online Resource 12). Seven [31, 33, 34, 69, 76, 81, 82] out of ten studies reported a significant association between either low MNA or low MNA-SF and low BI or low FIM. One study [30] did not show an association and in two studies [54, 64] heterogeneous outcomes were observed. Higher BMI values (in the normal to overweight range) were significantly associated with higher scores of the BI [68] and the FIM [64] in one study each. However, five [31, 54, 57, 66, 69] out of seven studies did not indicate significant associations between BMI and either BI or FIM (Online Resource 13).

Discussion

The aim of this systematic literature review and meta-analysis was to present an overview of the nutritional status on admission and its association with functional parameters in geriatric rehabilitation patients. The pooled prevalence (95% CI) for MNA (nine studies) demonstrated that malnutrition and risk of malnutrition were present in 13% (5–20) and 47% (40–54) of the geriatric rehabilitation population, whereas the pooled estimate (95% CI) of BMI ($n=45$) was 23.8 kg/m² (23.2–24.5). The ranges of the values and heterogeneity were high among the individual studies of the respective pooled estimates. Malnutrition

and risk of malnutrition according to MNA or MNA-SF were significantly associated with lower levels of BI and FIM in the majority of studies (seven out of ten) reporting it, whereas significant associations between BMI and BI or FIM were observed in only two out of seven studies.

The high pooled prevalence of malnutrition and risk of malnutrition according to MNA confirm earlier findings from a meta-analysis with slightly higher pooled prevalence (95% CI) of 29% (22–37) for malnutrition and 49% (42–55) for risk of malnutrition [83]. However, heterogeneity was high, which limits the interpretation of these results. Compared to other settings, the prevalence of malnutrition (MNA) in geriatric rehabilitation is slightly lower than in hospital patients (18%) and in nursing home residents (22%), but higher than in the community-dwelling older people (3%) [83]. In the included studies, a large variety of screening tools, e.g., MNA-SF, MUST, PG-SGA, with a large diversity in screening criteria was applied in addition to the MNA, which resulted in an even wider range of malnutrition prevalence (6–88%). Our findings emphasize the need for a more standardized and age-specific approach towards nutritional screening in geriatric rehabilitation patients. Findings for the pooled estimates of BMI show that the vast majority of the geriatric rehabilitation population had mean BMI values in the normal or overweight range. BMI values were, as expected, lowest in Asia. Although mean BMI is normal, a considerable percentage (0–17%) of the geriatric rehabilitation population had BMI values in the underweight range. Prevalence of obesity was not reported in any study. This would have been highly relevant information in this population, as obesity also has a relevant impact on functionality [7]. However, the high prevalence of malnutrition and risk of malnutrition combined with an average normal to high BMI indicates that a BMI is not a good proxy for malnutrition, and that screening for malnutrition with a validated screening tool should be used to identify those with malnutrition, and treat accordingly.

A wide range of indices for body composition were reported, but most studies applied bioelectrical impedance analysis. However, the high heterogeneity in body composition parameters does not allow an overall conclusion in this regard. Sarcopenia was addressed by only two studies that observed high prevalence (40–76%) suggesting that low muscle mass is prevalent in the geriatric rehabilitation population. This is comparable to the prevalence reported in another systematic review, 56 (46–65) % in rehabilitation inpatients [13]. It was higher than in community-dwelling seniors where the prevalence was 10% [84] but comparable to older medical patients with older age with prevalence rate up to 40% [85–87].

The pooled estimate of 34.1 g/L for albumin indicates that a substantial part of the geriatric rehabilitation population has albumin levels below the reference range for

healthy, non-malnourished individuals (35–45 g/L) [88]. We included albumin as it was indicated as a nutritional marker in the included studies. The value of albumin as a marker for nutritional status or malnutrition, however, is limited because of its sensitivity to inflammatory stress [89, 90]. Regarding nutrient intake, data were limited to a few studies that indicated that energy and protein intake, as well as vitamin D status, was low in the geriatric rehabilitation population. Information on micronutrient levels in blood was limited, indicating a knowledge gap in this aspect of nutritional status and potential unmet nutritional needs in this population.

We observed a positive association between nutritional status (MNA and MNA-SF) with functional status (BI and FIM). Our findings are in line with results observed in other patient groups [8, 9, 20, 91]. Information on the association between BMI and functional status were contradictory. This might be because BMI and functional status showed a U- or J-shaped curve in other populations with optimal BMI values between 20 and 30 kg/m² [92].

Our findings emphasize that in addition to malnutrition screening, screening for sarcopenia would benefit this population as a structured approach to manage malnutrition and muscle loss could improve muscle mass and functional outcomes [93]. It is also known that a higher protein intake (1.0–1.2 g/kg bw/day) and an adequate energy intake can prevent disability in higher age [3].

Screening should be followed by an appropriate dietary intervention in geriatric rehabilitation patients, focusing on age-specific energy and protein recommendations and treatment of vitamin D deficiency where necessary. This approach may allow patients to regain muscle mass and muscle strength which will enhance functional recovery. However, this is also a field for further research as high-quality studies are scarce.

The quality of reporting on measurements was high in most included studies. The applied measurement tools were objective, reliable and valid as this was a selection criterion for nutritional outcome measurements. Potential confounders were considered in statistical analysis in one-third of the studies. Limitations in study quality were seen for sample size calculation, description of the study population and consideration of potential confounders.

One of the strengths of our systematic review is the comprehensive inclusion of data on the geriatric rehabilitation populations around the world in a systematic selection and review process according to the PRISMA guideline, based on a study protocol with predefined inclusion and exclusion criteria. The primary literature search was not limited by publication year. We focused on both nutritional and functional status and add relevant information to the current knowledge of the characteristics of geriatric rehabilitation patients.

This review also has several limitations. Eligible studies had to report at least on nutritional status. This implies that the present paper does not provide a complete overview on functional status in geriatric rehabilitation patients. A further limitation is the MNA as the only malnutrition screening tool in the meta-analysis due to scarce data for other malnutrition screening tools like the new ESPEN and Global Leadership Initiative on Malnutrition (GLIM) tools [94, 95]. In particular, the prevalence of ESPEN and GLIM malnutrition is a highly relevant topic for future research. The large heterogeneity of geriatric rehabilitation settings across the world often lacking a clear description may be seen as another limitation. Our findings therefore show that geriatric rehabilitation has not been clearly defined yet.

Conclusions

A relevant percentage of the geriatric rehabilitation population is affected by malnutrition and risk of malnutrition, vitamin D deficiency and low protein intake. The majority of geriatric rehabilitation patients have BMI values in the normal or overweight range. Malnutrition is associated with a low functional status. These findings emphasize the need for malnutrition screening followed by appropriate dietary interventions in geriatric rehabilitation patients. The latter should focus on age-specific energy and protein recommendations and treatment of vitamin D deficiency where necessary. This approach may allow patients to regain muscle mass and muscle strength which will enhance functional recovery. Future studies in this field should include a standardized set of nutritional and functional parameters to facilitate data comparison.

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Compliance with ethical standards

Conflict of interest There are conflicts of interest related to the manuscript: JvW, CVDB, ACY, YL are employees of Danone Nutricia Research; JW and RD report grants from Danone Nutricia, outside the submitted work; JB reports personal fees from Fresenius, Nestlé, Novartis, Pfizer, Bayer, and grants and personal fees from Danone Nutricia, outside the submitted work.

Ethical approval Not applicable.

Informed consent Not applicable.

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