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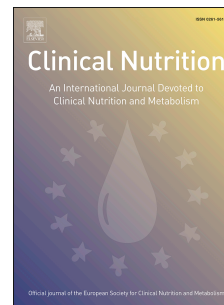
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Potentially Modifiable Determinants of Malnutrition in Older Adults: a Systematic Review

M. O'Keeffe, M. Kelly, E. O'Herlihy, P.W. O'Toole, P.M. Kearney, S. Timmons, E. O'Shea, C. Stanton, M. Hickson, Y. Rolland, C. Sulmont Rossé, S. Issanchou, I. Maitre, M. Stelmach-Mardas, G. Nagel, M. Flechtner-Mors, M. Wolters, A. Hebestreit, L.C. De Groot, O. van de Rest, R. Teh, M.A. Peyron, D. Dardevet, I. Papet, K. Schindler, M. Streicher, G. Torbahn, E. Kiesswetter, M. Visser, D. Volkert, E.M. O'Connor, on behalf of the MaNuEL consortium

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1 Potentially Modifiable Determinants of Malnutrition in Older Adults: a 2 Systematic Review

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45 **Abstract**

46 **Background & Aims:** Malnutrition in older adults results in significant personal, social, and
47 economic burden. To combat this complex, multifactorial issue, evidence-based knowledge is
48 needed on the modifiable determinants of malnutrition. Systematic reviews of prospective studies
49 are lacking in this area; therefore, the aim of this systematic review was to investigate the
50 modifiable determinants of malnutrition in older adults.

51 **Methods:** A systematic approach was taken to conduct this review. Eight databases were searched.
52 Prospective cohort studies with participants of a mean age of 65 years or over were included.
53 Studies were required to measure at least one determinant at baseline and malnutrition as outcome
54 at follow-up. Study quality was assessed using a modified version of the Quality in Prognosis
55 Studies (QUIPS) tool. Pooling of data in a meta-analysis was not possible therefore the findings of
56 each study were synthesized narratively. A descriptive synthesis of studies was used to present
57 results due the heterogeneity of population source and setting, definitions of determinants and
58 outcomes. Consistency of findings was assessed using the schema: strong evidence, moderate
59 evidence, low evidence, and conflicting evidence.

60 **Results:** Twenty-three studies were included in the final review. Thirty potentially modifiable
61 determinants across seven domains (oral, psychosocial, medication and care, health, physical
62 function, lifestyle, eating) were included. The majority of studies had a high risk of bias and were of
63 a low quality. There is moderate evidence that hospitalisation, eating dependency, poor self-
64 perceived health, poor physical function and poor appetite are determinants of malnutrition.
65 Moderate evidence suggests that chewing difficulties, mouth pain, gum issues co-morbidity, visual
66 and hearing impairments, smoking status, alcohol consumption and physical activity levels,
67 complaints about taste of food and specific nutrient intake are not determinants of malnutrition.
68 There is low evidence that loss of interest in life, access to meals and wheels, and modified texture

69 diets are determinants of malnutrition. Furthermore, there is low evidence that psychological
70 distress, anxiety, loneliness, access to transport and wellbeing, hunger and thirst are not
71 determinants of malnutrition. There appears to be conflicting evidence that dental status,
72 swallowing, cognitive function, depression, residential status, medication intake and/or
73 polypharmacy, constipation, periodontal disease are determinants of malnutrition.

74

75 **Conclusion:** There are multiple potentially modifiable determinants of malnutrition however strong
76 robust evidence is lacking for the majority of determinants. Better prospective cohort studies are
77 required. With an increasingly aging population, targeting modifiable factors will be crucial to the
78 effective treatment and prevention of malnutrition.

79

80 **Keywords:** malnutrition, determinants, older adults, systematic review, prospective cohort studies

81

82 **INTRODUCTION**

83

84 Malnutrition is defined as “a state of nutrition in which a deficiency of energy, protein and other
85 nutrients causes measurable adverse effects on tissue and body form (body shape, size and
86 composition) and function and clinical outcome” [1]. Protein-energy malnutrition in particular, is
87 common, costly and increases with age, resulting in significant personal, social and economic
88 burden [1, 2]. Of most concern, it is an increasing health problem, mainly due to changes in
89 worldwide population demographics. For instance, between 2010 and 2050, the global population
90 over the age of 80 has been predicted to grow from 11.5% to 21.0% worldwide and from 9.0% to
91 19.0% in developed countries [3]. The prevalence of malnutrition in older adults varies significantly
92 across different population subgroups; it is higher in older persons with higher disability levels,
93 deteriorating health and multi-morbidities, deteriorating poor physical function, and dependence in
94 activities of daily living (ADL) [4]. Malnutrition affects less than 10% of independently living older
95 persons in the community. This prevalence is even lower when older adults are living at their home
96 and attending senior centres [5, 6]. However, the prevalence is reported to be 50% higher in nursing
97 home and acute care settings; estimates ranging from 30-50% [7-9], displaying the importance of
98 examining malnutrition across multiple settings. Although malnutrition is a prognostic factor
99 associated with morbidity, mortality, and costs of care, nutritional problems in older adults often
100 remain undetected or unaddressed [10]. This is a serious issue, as malnutrition is strongly associated
101 with sarcopenia and frailty, two major public health issues among older adults [2, 11].
102 Understanding the aetiology of malnutrition, and finding effective interventions and preventive
103 strategies is therefore of utmost importance [12-14].

104

105 Several different definitions and criteria have been recommended for the diagnosis of malnutrition.
106 These include different cut-off points for weight loss, body mass index (BMI), blood parameters
107 (e.g. albumin) and assessment tools (e.g. the full Mini Nutritional Assessment (MNA)) [15-18]. The
108 heterogeneity across definitions and diagnostic criteria in research and clinical practice makes it
109 very difficult to generate meaningful data or comparisons on true malnutrition prevalence,
110 incidence and treatment response across different countries and settings. Nevertheless, focusing on
111 which factor contribute to the development of malnutrition may aid the development of effective
112 interventions.

113
114 Multiple factors have been correlated with malnutrition in older adults and then suspected to be
115 determinants including reduced appetite, female sex, social resources, poor physical function, poor-
116 self related health, sensory function, chewing and swallowing problems, physical and cognitive
117 impairment, depression, polypharmacy, low-grade inflammation, low socioeconomic status and
118 loneliness, lack of food choices, lack of dietary advice/education, and older age [2, 6, 15-20].
119 However, most of the available studies in this area are cross-sectional with limited ability to make
120 causal inference. Less emphasis has focussed on prospective studies and on determinants that could
121 be considered potentially modifiable. Achieving consensus on what determinants may be
122 modifiable, and generating strategies to modify these may be useful for future prevention and
123 treatment of malnutrition.

124
125 Several studies and narrative reviews describe determinants of malnutrition. To date, three
126 systematic reviews [14, 21, 22] have been completed in this area. One of these systematic reviews
127 [21] investigated the determinants of malnutrition in community adults only, and only up to January
128 2013. This review consisted of mainly cross-sectional studies; it excluded certain tools for

129 measuring malnutrition, and was limited to studies conducted in Western countries. The second [14]
130 of the three reviews investigated determinants of malnutrition in nursing home patients only, from
131 January 1990 to 2013 (16 cross-sectional studies). The third review [22] assessed determinants
132 using prospective cohort studies which were published between January 2000 and March 2015.
133 This review which had strict inclusion criteria based on sample size, measures of malnutrition, and
134 methods of statistical analysis and, included six studies. No systematic review of malnutrition in
135 older people has searched all years up to 2017, included all settings, was not restricted based on
136 definitions or outcome measures used, and was focussed on modifiable determinants, which are
137 arguably the most important for prevention and treatment of malnutrition. It is necessary to examine
138 all of the available evidence to achieve a better understanding of the determinants, and effectively
139 inform the design of future studies to generate better data and outcomes. Therefore, the objective of
140 this systematic review was to examine the potentially modifiable determinants of malnutrition in
141 older adults, across all settings, using information from prospective studies.

142

143 **METHODOLOGY**

144 **Search Strategy**

145 This review was registered on the PROSPERO database (CRD42017070383) and has been reported
146 in accordance with the PRISMA statement [23]. Relevant prospective cohort studies meeting the
147 inclusion criteria were identified by a computer aided search of the MEDLINE, CINAHL,
148 Academic Search Complete, AMED, SPORTDiscus, PsycINFO, Biomedical Reference Collection,
149 PsycARTICLES, and Web of Science databases during February 2017 from the period of inception
150 (See **Figure 1** for search keywords). The reference lists of the included manuscripts were searched
151 for additional papers by two independent reviewers. The search was restricted to include all studies

152 that involved humans and were published in English, French, Dutch or German only. The reference
 153 lists of the selected articles were also manually searched for any further relevant articles

154

155 Two reviewers (MOK and MK) screened the articles independently. The strategy had two
 156 components which were combined: (1) nutrition AND (2) old. The terms were searched using title
 157 and abstract. The exact search strings utilized are shown in **Figure 1**.

158

159 **Figure 1: Search keywords**

Nutrition* OR nutrient* OR undernutrition OR "under nutrition" OR undernourish* OR "under nourish*" OR under-nutrition OR malnutrition OR malnourish* OR "body composition" OR body-composition OR "underweight* OR "under weight" OR "weight loss" OR weight-loss OR underfed* OR "under fed" OR starv* OR weight* OR thinness OR sarcopeni* OR "energy intake" OR "food intake" OR anorexia* OR fasting* OR underfeeding OR hunger* OR BMI OR "body mass index" OR cachexia* OR "wasting syndrome" OR protein-energy OR protein-calorie OR "protein calorie" OR "protein energy" OR slimness OR diet* OR appetite* (Title and Abstract)
AND
old* OR elder* OR elderly OR geriatric* OR senior* OR aging* OR aged OR "old age" OR "nursing home" OR nursing-home OR "community dwell*" OR "community-dwell*" OR "home care" OR home-care OR domiciliary OR free-living OR "free living" OR "over age 65" OR "65 and over" OR "living at home" OR "home nurs*" OR "home living" OR home-living OR "home help" OR home-help OR "home health" OR home-health OR "long-term care" OR "long term care" OR "community care" OR "domestic care " OR "residential care" OR long-stay OR "long stay" (Title and Abstract)

160

161 **Inclusion/Exclusion Criteria**

162 *Study design*

163 Only reports of completed prospective cohort studies published in peer-reviewed journals were
164 included. Only prospective studies that looked at the impact of determinants on the evolution of
165 malnutrition were included.

167 ***Population***

168 Study participants were required to be 65 years or older (if a combined population was described,
169 the mean age had to be ≥ 65 years [24]). All settings (nursing home, community-dwelling, geriatric
170 rehabilitation setting, acute care setting) were included. Studies examining specific patient groups
171 (e.g. cancer patients) were not excluded based on the presence of these specific co-morbidities, as
172 co-morbidity is a known determinant of malnutrition.

174 ***Potential determinants***

175 Studies were required to examine one or more determinants of malnutrition. Studies examining
176 determinants that the authors of this review deem as potentially modifiable by the older adult or by
177 a carer-physician were included. Decisions on the potential modifiability of determinants were
178 based on consensus within the author group. Factors considered non-modifiable, like age and
179 genetics, were excluded. Attempts were made not to be too strict on what constituted non-
180 modifiable, as it remains unclear whether certain factors within particular settings, are modifiable or
181 not. Where it was unclear whether the factor was modifiable or non-modifiable (e.g. vision.
182 cognitive state), the study was included.

184 ***Clinical Outcomes***

185 Studies had to report results from an outcome measure in the domain of malnutrition. Examples
186 include BMI, and weight loss percentage. Since there is no gold standard definition or criteria for

187 malnutrition, no study was excluded based on the outcome measure used for malnutrition. This
188 means that studies that assessed malnutrition by screening or assessment tools (e.g. MNA and
189 MUST) that include risk factors of malnutrition were included. Differences in definitions and
190 criteria used for malnutrition were recorded. No restriction was placed on the time of follow-up.

191
192 A previous review [21] excluded studies that assessed malnutrition by screening or assessment tools
193 that include determinants of malnutrition (such as the MNA and the MUST). Therefore, we also
194 completed a descriptive synthesis without these studies to see if their removal would change the
195 results.

197 **Study selection**

198 A standard protocol was followed for study selection and data extraction. After the removal of
199 duplicates, two authors (MOK and MK) independently screened the titles and abstracts from the
200 articles found, and excluded articles not meeting the eligibility criteria. If no abstract was available,
201 or when it was not clear if the study should be included, full-text articles were retrieved in order to
202 determine inclusion or exclusion. Both reviewers kept a record of their reasons for the inclusion or
203 the exclusion of articles. The full-text version of an article was obtained if the title and abstract
204 seemed to fulfil the inclusion criteria, or if the eligibility of the study was unclear. If any
205 disagreements on study eligibility took place, the planned procedure was to hold a consensus
206 meeting with another author (EOC). Original study authors were emailed, where required, to
207 provide clarity on methodology.

208

209 **Risk of bias assessment and overall quality**

210 Two reviewers assessed the methodological quality of the studies independently and discrepancies
211 were resolved by consensus. If necessary, a third author helped to reach consensus. The
212 methodological quality was assessed by the Quality in Prognosis Studies (QUIPS) tool, which has
213 been recommended by the Cochrane Prognosis Methods Group [25]. The QUIPS was modified to
214 judge bias in relation to determinants, instead of the original tool's focus on prognostic factors. The
215 modified version has been used in a previous systematic review [26]. The following six domains
216 were considered: 1) study participation, 2) study attrition, 3) measures of risk factors, 4)
217 measurement of, and controlling for confounding variables, 5) outcome measures, 6) analysis and
218 reporting. Each domain was assessed as having high, moderate or low risk of bias (ROB) The
219 overall ROB was also assessed. We considered a study to be of high quality when the ROB was
220 rated low on at least four of the six domains and was rated low for both study attrition and study
221 confounding. This approach has been used for systematic reviews in other fields [26].

222

223 **Data extraction and data analysis**

224 Data regarding each study were extracted by one author (MOK) and cross-checked by a second
225 author (MK). The following data were extracted from each study:

- 226 - Characteristics of the determinant: domain, study and determinant examined
- 227 - Characteristics of the participants: setting, country, sample size, sex, age
- 228 - Characteristics of the outcome: malnutrition outcome measure and length of follow-up
- 229 -Results: for example, odds ratios, hazard ratio, risk ratio, 95% confidence intervals, p-values
- 230 -Study quality: overall rating on the QUIPs
- 231 -Strength of evidence: Low, Moderate, or High.

232 Due to substantial heterogeneity across studies, in terms of determinants examined, measurement of
233 determinants, definition of malnutrition, malnutrition measurement, and length of follow-up,

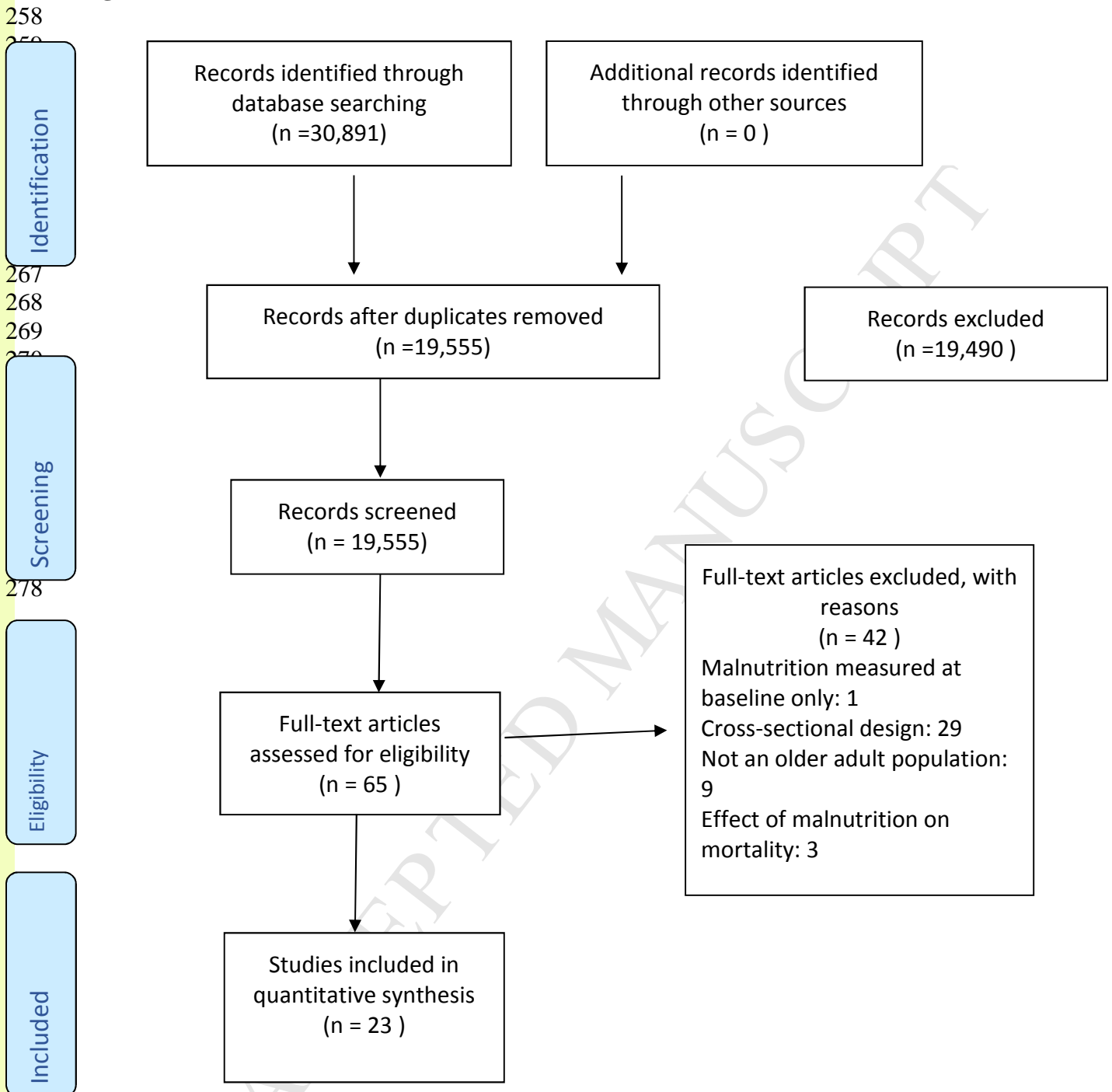
pooling of data in a meta-analysis was not possible. A descriptive synthesis [27] of studies was instead used to explore heterogeneity due to population source and setting, definitions of determinants and outcomes. Consistency of findings was assessed using the following schema.

- **Strong evidence:** consistent findings (defined as > 75% of studies showing the same direction of effect) in multiple high-quality (defined as low ROB in all domains) studies.
- **Moderate evidence:** consistent findings in multiple low quality (moderate to high ROB in 4 of 6 domains) studies and/or at least one low risk of bias/high-quality study.
- **Low evidence:** findings from one study only of moderate to high ROB (low or moderate quality).
- **Conflicting evidence:** inconsistent findings across studies of any risk of bias/quality.

RESULTS

Literature search

Study identification is summarised in **Figure 2**. The literature search of databases yielded **30,891** potentially relevant articles. 11,336 duplicates were removed and **19,555** titles and abstracts were scanned. Sixty five full-text studies were retrieved with 42 studies being excluded as they did not meet the eligibility criteria. Searching the reference lists of these articles did not yield any further articles. The major reasons for exclusion were cross-sectional design, mean age <65 years, and examined the association of malnutrition with mortality. Twenty three articles met the selection criteria. Two authors were emailed to obtain further information for clarification, of whom one replied.

257 **Figure 2: Flowchart**

279 **Quality assessment**

280 The majority of studies were rated as low quality on the QUIPS tool (n=18) [24-45]. Five studies
281 [46-49] were rated as moderate quality on the QUIPS tool. Common methodological limitations
282 identified across studies were attrition rates, study confounding, and statistical analysis and
283 reporting. Common methodological strengths were description of study participants and explanation
284 of potential determinant and outcome measurements. The quality assessment scores for all studies
285 are shown in **Table 1**.

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286 **Table 1: Risk of bias/quality scores**

Study	1	2	3	4	5	6	Final quality rating
Agostini et al 2004 [28]	Low	Low	Low	Low	Moderate	Low	Moderate
Alley et al 2010 [29]	Low	High	Low	High	Low	Low	Low
Beck et al 2015 [30]	Low	High	High	Low	High	High	Low
Carrión et al 2015 [31]	Low	High	Low	Low	High	High	Low
Chen et al 2009 [32]	Low	High	High	Low	High	High	Low
Izawa et al 2014 [33]	Low	High	Low	Low	Low	Low	Low
Johansson et al 2009a [34]	Low	High	Low	Low	High	Low	Low
Johansson et al 2009b [35]	Low	Moderate	Low	Low	High	High	Low
Jyrkkä et al 2011 [36]	Low	High	Low	Low	High	Low	Low
Kagansky et al 2005 [37]	Low	Moderate	Low	Low	High	High	Low
Knoops et al 2005 [38]	Low	Moderate	High	Low	High	Low	Low
Lee et al 2004 [39]	Low	Moderate	High	Low	High	High	Low
Mamhidir et al 2006 [40]	Low	High	High	High	High	High	Low
Okabe et al 2015 [41]	Low	Moderate	Low	Low	Low	Low	Moderate
Ritchie et al 2000 [42]	Low	Moderate	Low	Low	Low	Low	Moderate
Roberts et al 2007 [43]	Low	High	Low	Low	Low	Low	Low
Schilp et al 2011 [44]	Low	Moderate	Low	Low	Low	Low	Moderate
Serra-Prat et al 2012 [45]	Low	High	Low	Low	High	Low	Low
Shatenstein et al 2001 [46]	Low	Moderate	Low	Low	High	High	Low
Söderström et al 2015 [47]	Low	Moderate	Low	Low	High	High	Low
St-Arnaud McKenzie et al 2010 [48]	Low	Moderate	Low	Low	Low	Low	Moderate
Stephen and Janssen 2010 [49]	Low	High	Low	Low	High	Yes	Low
Weyant et al 2004 [50]	Low	Moderate	Low	Low	High	Low	Low

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High quality: risk of bias was rated low on at least four of the six domains and was rated low for both study attrition and study confounding (shaded).

Moderate quality: risk of bias was rated low or moderate on at least four of the six domains and was rated moderate for both study attrition and study confounding (shaded).

Low quality: risk of bias was rated high on at least four of the six domains and/or was related high for study attrition and study confounding (shaded).

Studies with high risk of bias for study attrition or study confounding were rated as low quality.

1= Study Participation; 2=Study Attrition; 3=Risk Factor Measurement; 4=Outcome Measurement; 5=Study Confounding; 6=Statistical Analysis and Reporting

287

288 **Participants and follow-ups**

289 **Table 2** shows the characteristics of the 23 included studies in this review. The follow-up
 290 period of studies varied from 24 weeks to 12 years. All studies were performed in a mixed
 291 sample of males and females. Studies were conducted in the USA (n=5) [28, 29, 39, 42, 50],
 292 Canada (n=4) [43, 46, 48, 49], Sweden (n=4) [34, 35, 40, 47], the Netherlands (n=2) [38, 44],
 293 Japan (n=2) [33, 41], Spain (n=2) [31, 45], Denmark (n=1) [30], Israel (n=1) [37], Finland
 294 (n=1) [36], and Taiwan (n=1) [32]. Studies involved participants from community-dwelling
 295 setting only (n=15) [28, 29, 34, 35, 39-45, 47-50], nursing home only (n=3) [30, 33, 38],
 296 acute hospital only (n=3) [31, 32, 37], and a combination of community-dwelling and nursing
 297 home settings (n=2) [36, 46]. The mean (SD) age across all studies was 74 (\pm 12) years.

298

299 **Definitions and measurement of malnutrition**

300 Table 2 shows the outcome measures used for malnutrition in the 23 included studies in this
 301 review. Type and cut-off for measures of malnutrition significantly varied across studies.
 302 Four studies [30, 38, 40, 44] used low BMI as a measure of malnutrition. However, the BMI
 303 cut off for being defined as malnourished varies across the four studies: one study [38] had no
 304 cut off; one study [30] defined <18.5 as malnourished; one study [40] defined <22 as
 305 malnourished, and one study [44] defined <20 as malnourished. Eight studies defined
 306 malnutrition by weight loss. Four studies [39, 46, 48, 50] used $>5\%$ loss of body weight as a

307 measure of malnutrition, but the time period of weight loss varied from one to two years
308 across studies. Two studies [42, 49] used >10% loss of body weight as a measure of
309 malnutrition. One study [28] used >10 pounds loss of body weight over a one-year period.
310 One study [29] used weight loss measured by DEXA as a measure of malnutrition. Two
311 studies [40, 44] used combinations of low BMI and weight loss to measure malnutrition.
312 Seven studies [31, 32, 34, 35, 37, 45, 47] used the long form MNA (MNA-LF). One of these
313 [45] defined <23.5 as malnourished, another [47] defined <17 as malnourished. Three studies
314 [33, 36, 41] used the short form MNA (MNA-SF). Two of these studies [33, 41] defined <7
315 as malnourished, while one study [36] defined <11 as malnourished. One study [43] used the
316 Elderly Nutrition Screening Tool.

317 **Table 2. Description of studies**

Domain	Study and determinant examined	Setting, country and participants	Malnutrition measure and length of follow-up	Results	Quality	Strength of evidence
Oral	Dental status					Conflicting
	Knoops et al 2005 [38]	Nursing home. Netherlands N=108 83% female Mean-age: 82.1(7.6)	BMI Follow-up: 24 weeks	NS	Low	
	Lee et al 2004 [39]	Community-dwelling. USA N=3075 52% female Mean age: unclear, ranged from 70-79	Weight loss \geq 5% of body weight in 1 year Follow-up: 1 year	NS	Low	
	Mamhidir et al 2006 [40]	Community-dwelling. Sweden N=503 72% female Mean age: 86.2(5.5)	BMI $<$ 22 and weight of 5% or 10% of total body weight Follow-up: 1 year	NS	Low	
	Okabe et al 2016 [41]	Community-dwelling. Japan N=197 Mean age: unclear	MNA- Short Form $<$ 7 Follow-up: 1 year	NS	Moderate	
	Ritchie et al 2000 [42]	Community-dwelling. USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss \geq 10% of body weight in 1 year Follow-up: 1 year	Edentulousness effect on 4% weight loss: OR (95% CI): 1.63 (1.09,2.43); P $<$ 0.05. Edentulousness effect on 10 % weight loss	Moderate	

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				OR (95% CI): 2.03 (1.05, 3.96); p<0.05		
	Roberts et al 2007 [43]	Community-dwelling. Canada N=839 68.7% female Mean age: 79.6	Elderly Nutrition Screening (6-13) Follow-up: 1 year	NS	Low	
	Chewing					Moderate
	Beck et al 2015 [30]	Community-dwelling. Denmark N=441 80% female Mean age: 85.2(7.5)	BMI<18.5 Follow-up: 6 months and 1 year	NS	Low	
	Izawa et al 2014 [33]	Nursing home. Japan N=392 77.7% female Mean age: 84.3(7.2)	MNA-Short Form <7 Follow-up: 2 years	NS	Low	
	Knoops et al 2005 [38]	Nursing home. Netherlands N=108 83% female Mean-age: 82.1(7.6)	BMI Follow-up: 24 weeks	NS	Low	
	Lee et al 2004 [39]	Community-dwelling. USA N=3075 52% female Mean age: unclear, ranged from 70-79	Weight loss ≥5% of body weight in 1 year Follow-up: 1 year	NS	Low	
	Mamhidir et al 2006 [40]	Community-dwelling. Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or 10% of total body weight Follow-up: 1 year	NS	Low	

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	Ritchie et al 2000 [42]	Community-dwelling. USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss \geq 10% of body weight in 1 year Follow-up: 1 year	NS	Moderate	
	Schilp et al 2011 [44]	Community-dwelling. Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Mouth Pain					Moderate
	Lee et al 2004 [39]	Community-dwelling. USA N=3075 52% female Mean age: unclear, ranged from 70-79	Weight loss \geq 5% of body weight in 1 year Follow-up: 1 year	NS	Low	
	Mamhidir et al 2006 [40]	Community-dwelling. Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or 10% of total body weight Follow-up: 1 year	NS	Low	
	Ritchie et al 2000 [42]	Community-dwelling USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss \geq 10% of body weight in 1 year Follow-up: 1 year	NS	Moderate	
	Gum issues					Conflicting
	Beck et al 2015 [30]	Community-dwelling.	BMI<18.5	NS	Low	

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		Denmark N=441 80% female Mean age: 85.2(7.5)	Follow-up: 6 months and 1 year			
	Ritchie et al 2000 [42]	Community- dwelling USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss \geq 10% of body weight in 1 year Follow-up: 1 year	NS	Moderate	
	Weyant et al 2004 [39]	Community- dwelling USA N=1053 50.3% female Mean age: 72.7(2.8)	Weight loss \geq 5% of body weight over 2 years Follow-up: 2 years	Extent of sites with \geq 6mm periodontal probing depth OR (95% CI): 1.53 (1.32-1.77); p<0.05.	Low	
	Swallowing					Conflicting
	Beck et al 2015 [30]	Community- dwelling, Denmark N=441 80% female Mean age: 85.2(7.5)	BMI<18.5 Follow-up: 6 months and 1 year	NS	Low	
	Carrión et al 2015 [31]	Acute hospital Spain N=1662 61.7% Female Mean age: 85.1(6.23)	MNA<17 Follow-up: 6 months and 1 year	OR (95% CI): 12.6 (7.49, 21.12); p<0.001	Low	
	Knoops et al 2005 [38]	Nursing home The Netherlands N=108 83% female Mean-age: 82.1(7.6)	BMI Follow-up: 24 weeks	NS	Low	
	Mamhidir et al 2006 [40]	Community- dwelling	BMI<22 and weight of 5% or10% of total	NS	Low	

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		Sweden N=503 72% female Mean age: 86.2(5.5)	body weight Follow-up: 1 year			
	Okabe et al 2016 [41]	Community-dwelling Japan N=197 Mean age: %female unclear	MNA- Short Form <7 Follow-up: 1 year	RR (95% CI): 5.21 (1.65, 16.43); p=0.005.	Moderate	
	Serra-Prat et al 2012 [45]	Community-dwelling Spain N=254 46.5% female Mean age: 78	MNA<23.5 Follow-up: 1 year	NS	Low	
Psychosocial	Cognitive function					Conflicting
	Chen et al 2009 [32]	Acute hospital Taiwan N=306 53.27% female Mean age: 71.75(5.62)	MNA<17 Follow-up: 6 months	B (SE): 0.17 (0.01), 95% CI (0.43, 0.60); p<0.001	Low	
	Johansson et al 2009a [34]	Community-dwelling Sweden N=579 % female Mean age: unclear	MNA<17 Follow-up: 6 years	NS	Low	
	Johansson et al 2009b [35]	Community-dwelling Sweden N=258 % female: unclear Mean age: 74.2(2.55)	MNA<17 Follow-up: 12 years (3 times with 4 year intervals)	For men: OR (95% CI): 12.9 (2.9, 56.7); p<0.01 For women: NS	Low	
	Kagansky et al 2005 [37]	Acute hospital Israel	MNA<17	OR (95% CI): 3.85 (1.55, 9.59);	Low	

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		N=414 65.7% female Mean age: 84.8(6.1)	Follow-up: 2 years	P=0.004.		
	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or 10% of total body weight Follow-up: 1 year	OR (95% CI): 1.844 (1.267, 2.683); P=0.001	Low	
	Okabe et al 2016 [41]	Community-dwelling Japan N=197 %female unclear Mean age: unclear	MNA- Short Form <7 Follow-up: 1 year	NS	Moderate	
	Ritchie et al 2000 [42]	Community-dwelling USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss ≥10% of body weight in 1 year Follow-up: 1 year	NS	Moderate	
	Roberts et al 2007 [43]	Community-dwelling Canada N=839 68.7% female Mean age: 79.6	Elderly Nutrition Screening (6-13) Follow-up: 1 year	NS	Low	
	Depression and depressive symptomology					Conflicting*
	Chen et al 2009 [32]	Acute hospital Taiwan N=306 53.27% female Mean age: 71.75(5.62)	MNA<17 Follow-up: 6 months	β (SE): -0.35 (0.03), 95% CI (-0.41, -0.29); p<0.0001	Low	
	Johansson et al 2009a	Community-	MNA<17	OR (95% CI):	Low	

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	[34]	dwelling Sweden N=579 % female: unclear Mean age: unclear	Follow-up: 6 years	1.522 (1.185, 1.954); p=0.001		
	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or10% of total body weight Follow-up: 1 year	NS	Low	
	Ritchie et al 2000 [42]	Community-dwelling USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss \geq 10% of body weight in 1 year Follow-up: 1 year	NS	Moderate	
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Shatenstein et al 2001 [46]	Community-dwelling and institutionalised Canada N=584 59.6% female Mean age: unclear, ranged from 70-90	Weight loss \geq 5% of body weight Follow-up: 5 years	Loss of interest in life For institution: β (SE): -0.63(0.29) 95% CI (0.30, 0.93); P=0.027 For community- dwelling β (SE): -0.58 (0.25) 95% CI (0.34,	Low	

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				0.90); p=0.017		
	Psychological distress					Low
	Roberts et al 2007 [43]	Community-dwelling Canada N=839 68.7% female Mean age: 79.6	Elderly Nutrition Screening (6-13) Follow-up: 1 year	NS	Low	
	Anxiety					Low
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Social support					Low
	Chen et al 2009 [32]	Acute hospital Taiwan N=306 53.27% female Mean age: 71.75(5.62)	MNA<17 Follow-up: six months	NS	Low	
	Roberts et al 2007 [43]	Community-dwelling Canada N=839 68.7% female Mean age: 79.6	Elderly Nutrition Screening (6-13) Follow-up: 1 year	NS	Low	
	Residential status					Conflicting
	Chen et al 2009 [32]	Acute hospital Taiwan N=306 53.27% female Mean age: 71.75(5.62)	MNA<17 Follow-up: six months	NS	Low	

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	Johansson et al 2009a [34]	Community-dwelling Sweden N=579 % female Mean age:	MNA<17 Follow-up: 6 years	NS	Low	
	Jyrkkä et al 2011 [36]	Community-dwelling and nursing home Finland N=294 69% female Mean age: 81.9	MNA- Short Form <11 Follow-up: 1, 2, 3 years	B (SE): -1.89 (0.25), 95% CI -2.38(-1.39); P<0.001	Low	
	Schilp et al 2011 [44]	Community-dwelling The Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Transport					Low
	Johansson et al 2009b [35]	Community-dwelling Sweden N=258 % female Mean age: 74.2(2.55)	MNA<17 Follow-up: 12 years (3 times with 4 year intervals)	NS	Low	
	Loneliness					Low
	Schilp et al 2011 [44]	Community-dwelling The Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Wellbeing					Low
	Johansson et al 2009a	Community-	MNA<17	NS	Low	

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	[34]	dwelling Sweden N=579 % female: unclear Mean age: unclear	Follow-up: 6 years			
	Meals on wheels					Low
	Johansson et al 2009b [35]	Community- dwelling Sweden N=258 % female Mean age: 74.2(2.55)	MNA<17 Follow-up: 12 years (3 times with 4 year intervals)	For men: OR (95% CI): 11.6 (2.0, 67.8); p<0.01 For women: OR (95% CI): 18.0 (1.8, 182.7); p<0.05.	Low	
Medication and care	Medication and polypharmacy					Conflicting
	Agostini et al 2004 [28]	Community- dwelling USA N=885 72% female Mean age: 81.0(5.2)	Weight loss \geq 10 pounds in 1 year Follow up: 1 year	1-2 medications: NS 3-4 medications: OR (95% CI): 1.96 (1.08, 3.54); p<0.05 \geq 5 medications: 2.78 (1.38, 5.60); p<0.05	Moderate	
	Beck et al 2015 [30]	Nursing home Denmark N=441 80% female Mean age: 85.2(7.5)	BMI<18.5 Follow-up: 6 months and 1 year	NS	Low	
	Chen et al 2009 [32]	Acute hospital Taiwan N=306 53.27% female Mean age: 71.75(5.62)	MNA<17 Follow-up: 6 months	β (SE)-0.08 (0.02), 95% CI (-0.13, - 0.04); p=0.0002	Low	

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	Jyrkkä et al 2011 [36]	Community-dwelling and nursing home Finland N=294 69% female Mean age: 81.9	MNA- Short Form <11 Follow-up: 1,2, 3 years	Excessive polypharmacy (10 or more drugs): β (SE): -0.62 (0.18); 95% CI -0.98(-0.27); p=0.001 Polypharmacy (6 to 9 drugs): NS	Low	
	Knoops et al 2005 [38]	Nursing home Netherlands N=108 83% female Mean-age: 82.1(7.6)	BMI Follow-up: 24 weeks	NS	Low	
	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or10% of total body weight Follow-up: 1 year	NS	Low	
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Hospitalisation					Moderate**
	Alley et al 2010 [29]	Community-dwelling USA N=2690 50.8% female Mean age: 73.5(2.9)	Weight loss per year in total body mass (DEXA scan) per year Follow-up: 1 year	For men: β (95% CI): -0.79 (-1.04, -0.54); p<0.001 For women: β	Low	

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				(95% CI): -0.79(-1.07, -0.51) p<0.001		
	Izawa et al 2014 [33]	Nursing home Japan N=392 77.7% female Mean age: 84.3(7.2)	MNA- Short Form <7 Follow-up: 2 years	OR (95%CI): 1.80 (1.09, 2.97); P=0.023	Low	
	Johansson et al 2009b [35]	Community-dwelling Sweden N=258 % female: unclear Mean age: 74.2(2.55)	MNA<17 Follow-up: 12 years (3 times with 4 year intervals)	For men: NS For women: OR (95% CI): 5.9(1.1, 31.5); p<0.05.	Low	
Health	Co-morbidities					Moderate
	Chen et al 2009 [32]	Acute hospital Taiwan N=306 53.27% female Mean age: 71.75(5.62)	MNA<17 Follow-up: 6 months	NS	Low	
	Izawa et al 2014 [33]	Nursing home Japan N=392 77.7% female Mean age: 84.3(7.2)	MNA- Short Form <7 Follow-up: 2 years	NS	Low	
	Jyrkkä et al 2011 [36]	Community-dwelling and nursing home Finland N=294 69% female Mean age: 81.9	MNA- Short Form <11 Follow-up: 1, 2, 3 years	NS	Low	
	Knoops et al 2005 [38]	Nursing home Netherlands	BMI	NS	Low	

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		N=108 83% female Mean-age: 82.1(7.6)	Follow-up: 24 weeks			
	Okabe et al 2016 [41]	Community-dwelling Japan N=197 Mean age: unclear %female unclear	MNA- Short Form <7 Follow-up: 1 year	NS	Moderate	
	Ritchie et al 2000 [42]	Community-dwelling USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss $\geq 10\%$ of body weight in 1 year Follow-up: 1 year	NS	Moderate	
	Roberts et al 2007 [43]	Community-dwelling Canada N=839 68.7% female Mean age: 79.6	Elderly Nutrition Screening (6-13) Follow-up: 1 year	NS	Low	
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss $\geq 5\%$ of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Functional health status					Conflicting
Constipation	Beck et al 2015 [30]	Nursing home Denmark N=441 80% female Mean age: 85.2(7.5)	BMI < 18.5 Follow-up: 6 months and 1 year	NS	Low	
Vision & hearing	Chen et al 2009 [32]	Acute hospital Taiwan	MNA < 17	Both NS	Low	

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		N=306 53.27% female Mean age: 71.75(5.62)	Follow-up: 6 months			
Constipation	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or 10% of total body weight Follow-up: 1 year	OR (95% CI): 2.490 (1.185, 4.964); p=0.015	Low	
Vision & hearing	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss ≥5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	Both NS	Moderate	
	Eating dependency/difficulty feeding					Moderate
	Beck et al 2015 [30]	Nursing home Denmark N=441 80% female Mean age: 85.2(7.5)	BMI<18.5 Follow-up: 6 months and 1 year	OR (95% CI): 2.16 (1.27, 3.67); p<0.05	Low	
	Knoops et al 2005 [38]	Nursing home Netherlands N=108 83% female Mean-age: 82.1(7.6)	BMI Follow-up: 24 weeks	NS	Low	
	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or 10% of total body weight Follow-up: 1 year	OR (95% CI): 2.257 (1.676, 3.038); p=0.001	Low	

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	Shatenstein et al 2001 [46]	Community-dwelling and nursing home Canada N=584 59.6% female Mean age: unclear, ranged from 70-90	Weight loss $\geq 5\%$ of body weight Follow-up: 5 years	β (SE): 4.24 (1.07); p=0.000	Low	
	Self-perceived health					Moderate***
	Johansson et al 2009a [34]	Community-dwelling Sweden N=579 % female: unclear Mean age: unclear	MNA<17 Follow-up: 6 years	OR (95% CI): 0.443 (0.289, 0.676); p<0.001	Low	
	Johansson et al 2009b [35]	Community-dwelling Sweden N=258 % female: unclear Mean age: 74.2(2.55)	MNA<17 Follow-up: 12 years (3 times with 4 year intervals)	For men: OR (95% CI): 3.9 (1.4, 10.8); p<0.01. For women: NS	Low	
	Jyrkkä et al 2011 [36]	Community-dwelling and nursing home Finland N=294 69% female Mean age: 81.9	MNA- Short Form <11 Follow-up: 1,2,3 years	Poor self-perceived health: β (SE): -1.05 (0.17), 95% CI -1.38-(-0.73); p<0.001	Low	
	Roberts et al 2007 [43]	Community-dwelling Canada N=839 68.7% female	Elderly Nutrition Screening (6-13) Follow-up: 1 year	OR (95% CI): 3.30 (1.42, 7.67)	Low	

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		Mean age: 79.6				
Physical function	ADL, performance or strength					Moderate
	Chen et al 2009 [32]	Acute hospital Taiwan N=306 53.27% female Mean age: 71.75(5.62)	MNA<17 Follow-up: 6 months	B (SE): 0.17 (0.01), 95% CI 0.15,0.19); P<0.001	Low	
	Izawa et al 2014 [33]	Nursing home Japan N=392 77.7% female Mean age: 84.3(7.2)	MNA Short-Form <7 Follow-up: 2 years	ADL score of 20-50 points: OR (95%CI): 2.62 (1.47, 4.69); P=0.001 ADL score of 0-15 points: OR (95% CI): 2.02 (1.10, 3.72); P=0.024	Low	
	Johansson et al 2009b [35]	Community-dwelling Sweden N=258 % female: unclear Mean age: 74.2(2.55)	MNA<17 Follow-up: 12 years (3 times with 4 year intervals)	For men: OR (95% CI): 7.5(2.8-20.4); p<0.001. For women: OR (95% CI): 3.3 (1.2, 9.2); p<0.05	Low	
	Knoops et al 2005 [38]	Nursing home Netherlands N=108 83% female Mean-age: 82.1(7.6)	BMI Follow-up: 24 weeks	β (95% CI): -0.11 (-0.21, -0.01); p=0.39.	Low	
	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female	BMI<22 and weight of 5% or 10% of total body weight Follow-up: 1 year	OR (95% CI): 1.793 (1.163, 2.765); p=0.008	Low	

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		Mean age: 86.2(5.5)				
	Okabe et al 2016 [41]	Community-dwelling Japan N=197 Mean age: unclear %female: unclear	MNA-Short Form <7 Follow-up: 1 year	NS	Moderate	
	Ritchie et al 2000 [42]	Community-dwelling USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss $\geq 10\%$ of body weight in 1 year Follow-up: 1 year	Dependent in one or more ADLs effect on 10% weight loss : OR (95% CI): 2.27 (1.08, 4.78); $p < 0.05$ NS for 4% weight loss	Moderate	
	Roberts et al 2007 [43]	Community-dwelling Canada N=839 68.7% female Mean age: 79.6	Elderly Nutrition Screening (6-13) Follow-up: 1 year	NS	Low	
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss $\geq 5\%$ of body weight in 6 months Follow-up: every 3 years over a 9 year period	Difficulty walking stairs, aged <75 HR (95% CI): 1.91 (1.14, 3.22) Difficulty walking stairs ≥ 75 years: NS Limitation of normal activities due to a health problem: NS Physical performance test	Moderate	

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				score: NS		
	Serra-Prat et al 2012 [45]	Community-dwelling Spain N=254 46.5% female Mean age: 78	MNA<23.5 Follow-up: 1 year	NS	Low	
	St Arnaud-McKenzie et al 2010 [48]	Community-dwelling Canada N=1497 52.3% Female Mean age: unclear. Ranged from 67-84	Weight loss \geq 5% of body weight over 2 years Follow-up: 2 years	Worse baseline physical function predicted both weight loss and weight gain	Moderate	
Lifestyle	Smoking					Moderate
	Ritchie et al 2000 [42]	Community-dwelling USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss \geq 10% of body weight in 1 year Follow-up: 1 year	NS	Moderate	
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Alcohol					Moderate
	Ritchie et al 2000 [42]	Community-dwelling USA N=563 57.9% female Mean age: unclear.	Weight loss \geq 10% of body weight in 1 year Follow-up: 1 year	NS	Moderate	

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		range 70 and over				
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Physical activity					Moderate
	Ritchie et al 2000 [42]	Community-dwelling USA N=563 57.9% female Mean age: unclear, range 70 and over	Weight loss \geq 10% of body weight in 1 year Follow-up: 1 year	NS	Moderate	
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	NS	Moderate	
	Stephen and Janssen 2010 [49]	Community-dwelling. Canada N=4512 57.1% female Mean age: unclear	Weight loss \geq 10% of body weight Follow-up: Every year over a 8 year period	NS	Low	
Eating	Appetite/leaves food on plate					Moderate
	Beck et al 2015 [30]	Nursing home Denmark N=441 80% female Mean age: 85.2(7.5)	BMI<18.5 Follow-up: 6 months and 1 year	OR (95% CI): 2.36 (1.07, 5.18); p<0.05	Low	
	Knoops et al 2005 [38]	Nursing home Netherlands N=108	BMI Follow-up: 24 weeks	β (95% CI): -2.16 (-4.32, -0.01); p=0.49	Low	

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		83% female Mean-age: 82.1(7.6)				
	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or10% of total body weight Follow-up: 1 year	NS	Low	
	Schilp et al 2011 [44]	Community-dwelling Netherlands N=1120 51.% female Mean age: 74.1(5.7)	Weight loss \geq 5% of body weight in 6 months Follow-up: every 3 years over a 9 year period	HR (95% CI): 1.63 (1.02, 2.61); p<0.05	Moderate	
	Shatenstein et al 2001 [46]	Community-dwelling and nursing home Canada N=584 59.6% female Mean age: unclear, ranged from 70-90	Weight loss \geq 5% of body weight Follow-up: 5 years	Community-dwelling: β (SE): -1.52 (0.33), 95% CI 0.12, 0.42); P=0.000	Low	
	Complaints about taste of food					Moderate
	Beck et al 2015 [30]	Nursing home Denmark N=441 80% female Mean age: 85.2(7.5)	BMI<18.5 Follow-up: 6 months and 1 year	NS	Low	
	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or10% of total body weight Follow-up: 1 year	NS	Low	
	Nutrient intake and modified texture diets					Moderate
	Knoops et al 2005 [38]	Nursing home	BMI	Fat intake at	Low	

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		Netherlands N=108 83% female Mean-age: 82.1(7.6)	Follow-up: 24 weeks	baseline β (95% CI): 0.07 (0.01, 0.13); p=0.027		
	Okabe et al 2016 [41]	Community-dwelling Japan N=197 Mean age: unclear %female unclear	MNA- Short Form <7 Follow-up: 1 year	NS	Moderate	
	Söderström et al 2015 [47]	Community-dwelling Sweden N=725 51.6% Female, Mean age 66.7	MNA<17 Follow-up: 10 years	BMI of <25kg/m ² at baseline: Fat intake: OR (95% CI): 1.106 (1.020, 1.199); P=0.015.	Low	
	Hunger					Low
	Mamhidir et al 2006 [40]	Community-dwelling Sweden N=503 72% female Mean age: 86.2(5.5)	BMI<22 and weight of 5% or10% of total body weight Follow-up: 1 year	NS	Low	
	Thirst					Low
	Knoops et al 2005 [38]	Nursing home Netherlands N=108 83% female Mean-age: 82.1(7.6)	BMI Follow-up: 24 weeks	NS	Low	

318

OR= Odds ratio, HR= Hazard ratio, RR= Risk ratio, NS: Non-significant, CI: confidence interval, BMI: body mass index, MNA: Mini Nutritional Assessment, DEXA: Dual-energy X-ray absorptiometry, ADL: Activities of Daily Living.

*When studies using the MNA are removed from the analysis, the conflicting evidence for depression being a determinant of malnutrition changes to moderate evidence that depression is not a determinant of malnutrition.

** When studies using the MNA are removed from analysis, the moderate evidence for hospitalisation being a determinant of malnutrition changes to limited evidence that hospitalisation is a determinant of malnutrition.

*** When studies using the MNA are removed from the analysis, the moderate evidence for self-perceived health being a determinant of malnutrition changes to limited evidence that self-perceived health is a determinant of malnutrition.

38

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320 **Potentially modifiable determinants**

321 Thirty determinants categorised into seven domains shown in **Table 3**. The results will be
 322 discussed according to these domains for ease of clarity.

323

324 **Table 3: Domains of potentially modifiable determinants**

Domain name	Included determinants (n=30)
Oral	1. Dental status 2. Chewing 3. Mouth pain 4. Gum issues 5. Swallowing
Psychosocial	6. Cognitive function 7. Depression/depressive symptomology 8. Psychological distress 9. Anxiety 10. Social support 11. Residential status 12. Transport 13. Loneliness 14. Wellbeing 15. Meals on wheels
Medication and care	16. Medication and polypharmacy 17. Hospitalisation
Health	18. Co-morbidities 19. Functional health status 20. Eating dependency/difficulty feeding 21. Self-perceived health
Physical function	22. Activities of daily living, performance or strength
Lifestyle	23. Smoking 24. Alcohol 25. Physical activity
Eating	26. Appetite / leaves food on plate 27. Complaints about taste of food 28. Dietary factors – nutrient intake and modified texture diets 29. Hunger 30. Thirst

325

326 Oral domain

327 A total of 13 studies [30-33, 38-45, 50] studies examined 5 potential determinants in the oral
328 domain.

329

330 Dental status

331 Dental status (denture use, having teeth) was assessed by six studies [38-43]. Measurement of
332 dental status varied significantly across studies. Five studies [38-40, 42, 43] used single item
333 yes/ no questions: One study [40] used a yes/no response to some or all natural teeth lost and
334 not using dentures; one study [38] assessed whether dental status was complete or
335 incomplete; one study [39] assessed if participants had any remaining natural teeth; one study
336 [43] assessed the presence or absence of dental problems. One study [42] scored participants
337 based on number of dentures, no teeth or presence of natural teeth.

338

339 Chewing difficulties

340 Chewing difficulties was assessed by seven studies [30, 33, 38-40, 42, 44]. Five studies [30,
341 38-40, 42] used single item yes/no questions on able or unable to chew or presence or
342 absence of chewing problems. One study [33] categorised chewing difficulties into three
343 categories: difficulty chewing even soft food items (poor), difficulty chewing harder foods
344 (fair), and no difficulty chewing harder foods (good). Only one study [44] assessed biting and
345 chewing with a question 'Are you able to bite or chew hard food?' and categorised
346 participants into 'almost never', 'some of the time', no problem, 'often' or 'most of the time'.

347

348 Mouth pain

349 Mouth pain was assessed by three studies [39, 40, 42] using a single item yes/no question on
350 the presence or absence of mouth pain.

351

352 Gum issues

353 Gum issues (inflammation, bleeding, periodontal disease) were assessed by three studies [30,
354 42, 50]. One study [30] used a single item yes/no answer question to the presence or absence
355 of inflamed, swollen or bleeding gums. One study [42] assessed the number of participants
356 with gum bleeding, and percentage of sites with this bleeding.

357 Two studies assessed the effect of periodontal disease [42, 50]. One study [50] measured
358 mean depth and attachment loss, percentage of pockets with at least 6mm probing depth. The
359 other study [42] used a single item yes/no question to assess the presence or absence of
360 periodontal disease.

361 One study [32] assessed a combination of oral health factors together and could not be
362 categorised under any one determinant. This study used the 12-item General Oral Health
363 Assessment Index to assess oral health.

364

365 Swallowing

366 Swallowing was assessed by six studies [30, 31, 38, 40, 41, 45]. Measurement of swallowing
367 varied significantly across studies. Two studies [31, 45] used the volume viscosity test. Three
368 studies [30, 38, 40] used single item yes/no questions from The Resident Assessment
369 Instrument - Minimum Data Set (RAI-MDS) to the presence or absence of swallowing
370 problems. One study [41] used cervical auscultation to assess swallowing problems.

371 There is conflicting evidence that dental status, periodontal disease and swallowing are
372 determinants of malnutrition.

373 There is moderate quality evidence that chewing difficulties, mouth pain and gum issues are
374 not determinants of malnutrition.

375

376 **Psychosocial domain**

377 A total of ten studies [32, 34-37, 40-44, 46] examined ten determinants in the psychological
378 domain.

379

380 Cognitive function

381 Cognitive function was assessed by eight studies [32, 34, 35, 37, 40-43]. Four studies [32, 34,
382 35, 43] used a Mini-Mental State Examination (MMSE) measure to assess cognitive capacity,
383 one study [46] used the modified MMSE (3MS); one study [32] used the 11-item MMSE,
384 two studies [34, 35] used the full MMSE; one study [43] used the Adult Lifestyle and
385 Function Interview MMSE (ALFI-MMSE). The Clinical Dementia Rating Scale and
386 Cognitive Performance Scale were used by two studies [40, 41], respectively. One study [37]
387 used a single item yes/no question on the presence of dementia, and the MNA 2 subscore on
388 cognitive status. Another study [42] assessed mental status subjectively by getting the
389 interviewer to judge the participants' presence or absence of mild confusion. Memory
390 impairment affecting ADL function was assessed by one study [34] using a single item
391 yes/no question; "Do you believe you are having memory problems that have an impact on
392 your daily life?".

393

394 Depression and depressive symptomology

395 Depression and/or depressive symptomology was assessed by six studies [32, 40, 42, 44, 46].
396 Measures of depression varied significantly across studies. One study [40] used the
397 Depression Rating Scale. One study [32] used the Geriatric Depression Scale Short-Form.
398 One study [42] used the Geriatric Depression Long-Form. One study [44] used the Center for
399 Epidemiological Studies Depression Scale while another [46] used the Cambridge Mental
400 Disorders of the Elderly Examination questionnaire and a single item yes/no question on loss

401 of interest in life. Only one study [42] used a single item question “How often have you felt
402 downhearted and blue?”

403

404 Psychological distress

405 Psychological distress was assessed by one study [43] using L’Indice de détresse
406 psychologique de Santé Québec (IDPESQ-14) questionnaire.

407

408 Anxiety

409 Anxiety was assessed by one study [44] using the anxiety subscale of the Hospital Anxiety
410 and Depression Scale.

411

412 Social support

413 Social support was assessed by two studies [32, 43]. One study [32] used the six-item Social
414 Support Questionnaire-Short Form. The second study [43] used a single item yes/no question
415 on satisfaction with social support.

416

417 Residential status

418 Residential status was assessed by four studies [32, 34, 36, 44]. Two studies [32, 34] used a
419 single item yes/no question on living alone or not. One study [36] assessed whether
420 participants were living at home or in sheltered accommodation. The final study [44] assessed
421 whether participants were independent in living, receiving home care, or not independent
422 (including institutionalised).

423

424 Transport

425 Use of special transport services was assessed by one study [35] using a single item yes/no
426 question on the use of special transport services.

427

428 Loneliness

429 Loneliness was assessed by one study [44] using the Dutch validated loneliness scale.

430

431 Wellbeing

432 Wellbeing was assessed by one study [34] using the Philadelphia Geriatric Centre Multilevel
433 Assessment Instrument.

434

435 Meals on wheels

436 Meals on wheels was assessed by one study [35] using a single item yes/no question on use
437 of meals and wheels.

438

439 There is conflicting evidence that cognitive function, depression and residential status are
440 determinants of malnutrition.

441 Low evidence suggests that loss of interest in life and access to meals and wheels are
442 determinant of malnutrition.

443 There is also low evidence showing that psychological distress, anxiety, residential status,
444 loneliness, access to transport and wellbeing are not determinants of malnutrition.

445 Furthermore, there is low evidence that access to meals and wheels is a determinant of
446 malnutrition.

447

448 **Medication and care domain**

449 A total of ten studies [28-30, 32-34, 36, 38, 40, 44] examined two determinants in the
450 medication and care domain.

451 Medication and/or polypharmacy

452 Medication and/or polypharmacy was assessed by seven studies [28, 30, 32, 36, 38, 40, 44].
453 One study [30] assessed prescription medications, and polypharmacy was defined as the
454 consumption of over five prescription medications per day. The second study [36] defined
455 excessive polypharmacy as the use of ten or more drugs, polypharmacy as the use of six to
456 nine drugs, and non-polypharmacy as the use of five or less drugs concomitantly. A third
457 study [28] recorded all medication reported taken by participants on a regular basis, and
458 categorised participants into no medication use, 1 or 2, 3 or 4, or 5 or more drugs taken daily.
459 The fourth study [40] assessed the number of medications reported taken in the last seven
460 days. One study [44] assessed medication through three categories: no medication use; the
461 use of one or two medications; and the use of three or more medications. Another study [32]
462 assessed the number of prescriptions and over the counter medication that were taken
463 currently by participants. Finally, one study [38] assessed the frequency of medication use
464 and type of medicines reported taken.

465

466 Hospitalisation

467 Hospitalisation was assessed by three studies [29, 33, 35]. Two studies used a single item
468 yes/no question to hospitalisation over a 2-year period [33], and hospital stay during the last 2
469 months [35]. One study [29] assessed total days hospitalized in a given year and categorised
470 participants into no hospitalisation, 1-3 days hospitalised, 4-7 days hospitalised, or 8 or more
471 days hospitalised.

472

473 There is conflicting evidence that medication intake and/or polypharmacy is a determinant of
474 malnutrition while moderate evidence suggests that hospitalisation is a determinant of
475 malnutrition.

476 **Health domain**

477 A total of twelve studies [30, 32-36, 38, 40-44] examined four determinants in the health
478 domain.

479

480 Co-morbidities

481 Co-morbidity was assessed by eight studies. Two studies [33, 41] used the Charlson
482 Comorbidity Index. Four studies [32, 38, 42, 44] assessed number and type of
483 diagnosis/disease. One study [43] used the chronic disease score while another study [36]
484 used the Functional Comorbidity Index.

485

486 Functional health status

487 Visual and hearing impairments were individually assessed by two studies [32, 44]. Two
488 categories were created: 'none' and 'one or two items with some difficulty'. Constipation was
489 individually assessed by two studies [30, 40] using a single item yes/no question on the
490 presence of constipation.

491

492 Eating dependency/Difficulty feeding

493 Eating dependency was assessed by four studies [30, 38, 40, 46]. Two studies [30, 40] used
494 the single item yes/no question on eating dependency (whether the person was classified as
495 independent in eating and drinking) from the Resident Assessment Instrument-Minimum
496 Data Set (RAI-MDS). One study [38] used a single item yes/no question on able/not able to

497 bring food to mouth. The last study [46] categorised ability to eat unaided into, completely
498 unable, with some help, or without help.

499

500 Self-perceived health

501 Self-perceived health was assessed by four studies [34-36, 43]. Two studies [34, 35] used the
502 Nottingham Health Profile. One study [36] used a five-point scale and classified participants
503 into three health status categories: good (very good/good), moderate and poor (fairly poor).
504 One study [43] assessed current health status by getting participants to rate their own health
505 as very good, excellent or poor, and their current health status (worse, same, better) compared
506 to their own health one year earlier.

507

508 There is moderate evidence that co-morbidity, visual and hearing impairments are not
509 determinants of malnutrition.

510 There is also moderate evidence that eating dependency and poor self-perceived health are
511 determinants of malnutrition.

512 Conflicting evidence suggests constipation is a determinant of malnutrition.

513

514 **Physical function domain**

515 Physical function was assessed by 13 studies [32-34, 36, 38, 40-46, 48]. Measures focused on
516 ADL, performance, and strength. Three studies [33, 34, 46] used the 0-100 ADL Index. One
517 study [40] used a 4-18 ADL score. Another study [38] used the Zorg index (Care Index
518 Questionnaire). A third study [43] summed the number of reported physical problems in the
519 past year (problems with balance, feet, ankles). Finally, one study [36] used an eight-point
520 instrumental ADL tool.

521

522 One study [42] used a single yes/no question on independent/dependent in ADLs of walking,
523 bathing, dressing, toileting, transferring, and getting outside. Three studies [32, 41, 45] used
524 the Barthel Index. Two studies [44, 48] used a series of performance tests. One study [44]
525 used three performance tests (chair stands, tandem stand, walk tests, and difficulty walking
526 stairs), and rated performance on a scale, and the other study [48] used eight performance
527 tests: handgrip, bicep strength, quadriceps strength, chair stand test, two gait speed tests,
528 timed up and go test, and the one leg stand test.

529

530 There is moderate evidence that physical function is a determinant of malnutrition.

531

532 **Lifestyle domain**

533 A total of three studies [42, 44, 49] examined three determinants in the lifestyle domain.

534

535 Smoking

536 Smoking status was assessed by two studies [42, 44]. One study [42] used a single item
537 yes/no question to the smoking or chewing of tobacco, and categorised participants into
538 current smoker, former smoker or those who had never smoked. The second study [44]
539 categorised participants into 3 categories: current smoker, former smoker, or never a smoker.

540

541 Alcohol

542 Alcohol use was assessed by two studies [42, 44]. One study [44] assessed alcohol use on the
543 number of days per week drinking alcohol, and the number of alcohol consumptions each
544 time, and categorised participants into four categories: no alcohol, light, moderate, and (very)
545 excessive use of alcohol. The second study [42] assessed alcohol use using a yes or no single
546 item yes/no question on drinking alcohol 5 or more days per week.

547

548 Physical activity

549 Physical activity was assessed by three studies [42, 44, 49]. One study [42] defined physical
550 activity by whether participants walked one or more blocks each day. A second study [44]
551 assessed physical activity in the previous two weeks using the Longitudinal Aging Study
552 Amsterdam Physical Activity Questionnaire which included information on frequency and
553 duration of walking, cycling, household activities, and sport activities. The third study [49]
554 asked participants whether they had engaged in common leisure activities in the previous 2
555 weeks, including walking, hiking, jogging, cycling, dancing, aerobics, bowling, golfing,
556 calisthenics, and swimming. Each activity was assigned a per-minute caloric expenditure
557 value, which was summed over all minutes of activity over the week.

558

559 There is moderate evidence that smoking status, alcohol consumption and physical activity
560 levels are not determinants of malnutrition.

561

562 **Eating domain**

563 A total of eight studies [30, 34, 38, 40, 41, 44, 46, 47] examined five determinants in the
564 eating domain.

565

566 Appetite/leaves food on plate

567 Appetite/leaving food on plate was measured by five studies [30, 38, 40, 44, 46]. Four studies
568 [30, 38, 40, 46] used a single item yes/no question on loss of appetite/leaves 25% of food on
569 plate or not. The other study [44] used the question 'I did not feel like eating, my appetite was
570 poor' from the Center for Epidemiologic Studies Depression Scale, and participant had to rate
571 on a 4-point scale.

572

573 Complaints about taste of food

574 Complaints about taste was assessed by two studies [30, 40]. Both studies used the single
575 item yes/no question on complaint/no complaint about taste of food from the RAI-MDS.

576

577 Dietary factors: Nutrient intake and modified texture diets

578 Two studies [38, 47] assessed energy and/or nutrient intake. One study [38] recorded
579 participant food and beverage consumption in diaries, and energy and nutrient intake (protein,
580 fat, carb) was calculated using the Dutch food composition database. The second study [47]
581 used a questionnaire assessing dietary intake, with a particular focus on fat, and the different
582 types of fat.

583 One study [41] assessed the effect of a modified texture diet (whether the diet was minced
584 into small pieces, pureed, or mixed in a blender).

585

586 Hunger

587 Hunger was assessed by one study [40] using a single item yes/no question from the RAI-
588 MDS on feeling hungry or not.

589

590 Thirst

591 Thirst was assessed by one study [38] by asking participants whether their thirst was
592 increased, normal or diminished.

593

594 There is moderate evidence that poor appetite is a determinant of malnutrition.

595 Moderate evidence suggests that complaints about taste of food and specific nutrient intake

596 are not determinants of malnutrition.

597 There is also low evidence that modified texture diets is a determinant of malnutrition.

598 Low evidence suggests that hunger and thirst are not determinants of malnutrition.

599

600

601 ***Results when studies using the MNA are removed***

602

603 Removing the ten studies [31-37, 41, 45, 47] which used the MNA as a indicator of
604 malnutrition changed the results for certain domains, because potential determinants are
605 included as part MNA. The conflicting evidence for depression changed to moderate
606 evidence that depression is not a determinant. The current moderate evidence for self-
607 perceived health and hospitalisation being determinant changed to limited evidence for both.
608 The evidence for the other potential determinants stayed the same.

609

610 Discussion

611
612 This systematic review provides moderate evidence that hospitalisation, eating dependency,
613 poor self-perceived health, poor physical function and poor appetite are determinants of
614 malnutrition.

615
616 There is moderate quality evidence that chewing difficulties, mouth pain, gum issues co-
617 morbidity, visual and hearing impairments, smoking status, alcohol consumption and
618 physical activity levels, complaints about taste of food and specific nutrient intake are not
619 determinants of malnutrition.

620
621 Low evidence suggests that loss of interest in life, access to meals and wheels, and modified
622 texture diets are determinants of malnutrition.

623 Furthermore, low evidence suggests that psychological distress, anxiety, loneliness, access to
624 transport and wellbeing, hunger and thirst are not determinants of malnutrition.

625
626 There is conflicting evidence that dental status, swallowing, cognitive function, depression,
627 residential status, medication intake and/or polypharmacy, constipation, periodontal disease
628 are determinants of malnutrition. The findings of this systematic review are broadly in line
629 with previous systematic reviews conducted on determinants of malnutrition in older adults
630 [14, 21, 22], but vary on the quality assessment of studies and the balance of evidence for
631 certain determinants. Two of these reviews [14, 22] state that certain factors, for example,
632 depression, swallowing, excessive polypharmacy are determinants of malnutrition, whereas
633 we have found that there is conflicting evidence for these potential determinants.

634

635 The results of this systematic review should be interpreted with caution due to the identified
636 limitations of the included studies. While prospective cohort studies are regarded as Level 1a
637 evidence, observational studies are often flawed by residual and unmeasured confounding.
638 The definitions and criteria used for malnutrition varied across studies, even within the same
639 domain (e.g. oral domain). Using the MNA as an outcome measure of malnutrition could
640 potentially lead to an overestimate of the impact of certain factors which are already in the
641 MNA. This aspect does not seem to be considered by authors of the included studies. We
642 examined if removal of the MNA studies would change the results and found that the items
643 which are part of the MNA (e.g. cognition, depression, physical function) were overestimated
644 in terms of their impact on determining malnutrition.

645

646 There is still no consensus on whether low BMI, malnutrition screening tools instead of
647 MNA, and percent weight loss, are equally valid and sensitive for measuring malnutrition
648 [51-53]. It is imperative that future research examines these considerations carefully, as a
649 better understanding of the best definition, is likely to significantly progress the quality of our
650 studies, and the overall malnutrition field [9, 55].

651

652 There is strong evidence that the prevalence of malnutrition varies across settings [2, 5, 6].
653 The vast majority of studies included in this review focus on the community setting. Due to
654 the paucity of literature focusing on the nursing home and acute hospital setting, it is difficult
655 to state with any certainty if different determinants of malnutrition are more relevant in
656 specific settings. Studies that examine the same determinants across multiple setting are
657 needed to enable any conclusions about setting-specific determinants.

658

659 Measurement of determinants across available studies varied significantly. Although
660 subjective complaints may be more relevant with regards to eating problems, most studies
661 poorly described the assessment of their determinants, and used single-item subjective
662 questions of questionable validity to measure determinants which may warrant objective
663 measurement (e.g. oral health, physical activity). Similar to the definition of malnutrition,
664 there is no consensus on what best defines cut-offs for certain determinants; for example,
665 good oral health, polypharmacy, cognitive function, etc. Research needs to better examine
666 what are the best definitions and measurements of these individual determinants.

667
668 There is a paucity of literature on certain determinants like hunger, physical activity, anxiety,
669 loneliness, social support, etc. with only one to two studies examining these factors; this
670 limited data means we cannot draw inference on these factors and malnutrition.

671
672 While we are interested in progressing our knowledge of malnutrition in older adults,
673 focusing on older adults with a mean age of 74 is also a significant limitation. Participants in
674 the included studies had high levels of co-morbidities at baseline, and the possibility that
675 malnutrition could have been present at baseline cannot be ruled out. Fifty years of age and
676 older has been defined as the new age bracket for older adults by some groups, so potentially
677 we need future research in older adults earlier in this range to track determinants and
678 malnutrition more closely over regular follow-ups, to give us a clearer understanding of the
679 true determinants of malnutrition in this population. Results may also be influenced by the
680 type of participants. We compared cohorts of different age, different settings, and different
681 health status so the determinants could change depending on the group under investigation.
682 Long term prospective studies are need recruiting participants from young old group before
683 they become malnourished to truly identify determinants of malnutrition. Future research in

684 specific age brackets, different settings and health status need to be conducted with
685 appropriate follow-ups to advance our understanding of the determinants of malnutrition in
686 different subgroups and settings as certain determinants are more relevant/specific depending
687 on the setting they are assessed in.

688
689 Analysing the effect of single determinants in isolation may have limitations. The emerging
690 international consensus on malnutrition is that it is a complex multidimensional problem
691 where determinants from different domains (e.g. oral, psychosocial, physical, lifestyle,
692 health, and eating) interact with each other, may vary from individual to individual, or over
693 time depending how strong the determinant is [56-60]. Treatments targeting a range of these
694 factors seem promising [61]. If determinants are not mutually exclusive, the utility of further
695 prospective studies analysing one determinant in isolation should be called into question.
696 Studies measuring the cumulative risk of different determinants may provide us with better
697 insights. Interactions between determinants should also be explored (for example, lack of
698 cooking skills might only be a determinant of malnutrition in older community-dwelling men
699 when they are recently widowed) which may be pertinent in different settings/genders.
700 Further research into multidimensional screening tools that measure cumulative risk across
701 multiple domains may be a useful way forward. It may then be worth examining if stratifying
702 or individualizing care based on the dominant modifiable determinants for each individual
703 can provide superior outcomes over one size fits all usual care approaches for malnutrition.

704
705 Strengths of this review are that it was systematically performed by two independent
706 reviewers, and only prospective cohort studies were included. We acknowledge some
707 limitations. (1) Our definition of a potentially modifiable determinant is open to
708 interpretation. Currently, we lack the data to confirm which determinants are modifiable. For

709 example, cognitive status, hospitalisation, medication, for a number of reasons, may not be
710 modifiable. We also do not know what underlying determinants influence the success of an
711 [nutritional] intervention, e.g. dental condition, ability to masticate and swallow food with
712 ease and mediate treatment response. However, placing more attention on factors that are
713 likely to be more modifiable, and treatable malnutrition, are important research and clinical
714 priorities (2). The way we categorised domains and determinants is subjective in nature.
715 Certain determinants (e.g. swallowing, self-reported health, dependency) are multifaceted in
716 nature, and so could also be placed in a different domain, as we do not understand the factors
717 that underlie these individual determinants. However, a previous review on this topic used a
718 similar categorisation approach [21]. We included studies with a wide variety of settings,
719 determinants, definitions, follow-up periods, and measurements, so it is difficult to synthesize
720 this heterogeneous evidence. However, we did use a descriptive synthesis [27] to give a best
721 evidence approach. Furthermore, definitions and measurements vary widely in clinical
722 practice. Lastly, the total number of presently available studies, especially when taking into
723 account the substantial heterogeneity between studies together with their inconsistent results,
724 is too limited to draw firm conclusions.

725

726 **Conclusion**

727 This systematic review of prospective studies provides moderate evidence that
728 hospitalisation, eating dependency, poor self-perceived health, physical function, poor
729 appetite are determinants of malnutrition. Moderate quality evidence suggests that chewing
730 difficulties, mouth pain, gum issues co-morbidity, visual and hearing impairments, smoking
731 status, alcohol consumption and physical activity levels, complaints about taste of food and
732 specific nutrient intake are not determinants of malnutrition. The review displays low
733 evidence that loss of interest in life, access to meals and wheels, and modified texture diets

734 are determinants of malnutrition, and low evidence that psychological distress, anxiety,
735 loneliness, access to transport and wellbeing, hunger and thirst are not determinants of
736 malnutrition. Finally, there is conflicting evidence that dental status, swallowing, cognitive
737 function, depression, residential status, medication intake and/or polypharmacy, constipation,
738 periodontal disease is a determinant of malnutrition. Overall multiple factors contribute to
739 malnutrition. However, strong robust evidence is lacking for many determinants. Better
740 prospective cohort studies are required. With an increasingly aging population, targeting
741 modifiable factors will be crucial to the effective treatment and prevention of malnutrition.

742

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756

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758 MV, DV and EMOC conceived the idea for the review. MOK and MK performed the
 759 database searches and analyses. MOK wrote the manuscript. All authors edited the
 760 manuscript. All authors have read and approved the final manuscript.

761

762 CONFLICT OF INTEREST

763 The authors declare no conflict of interest.

764

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Comment citer ce document :

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