Association of anorexia/appetite loss with malnutrition and mortality in older populations: A systematic literature review

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Abstract

Anorexia/appetite loss in older subjects is frequently underrecognized in clinical practice, which may reflect deficient understanding of clinical sequelae. Therefore, we performed a systematic literature review to assess the morbidity and mortality burden of anorexia/appetite loss in older populations. Following PRISMA guidelines, searches were run (1 January 2011 to 31 July 2021) in PubMed, Embase® and Cochrane databases to identify English language studies of adults aged ≥ 65 years with anorexia/appetite loss. Two independent reviewers screened titles, abstracts and full text of identified records against pre-defined inclusion/exclusion criteria. Population demographics were extracted alongside risk of malnutrition, mortality and other outcomes of interest. Of 146 studies that underwent full-text review, 58 met eligibility criteria. Most studies were from Europe (*n* = 34; 58.6%) or Asia (*n* = 16; 27.6%), with few (*n* = 3; 5.2%) from the United States. Most were conducted in a community setting (*n* = 35; 60.3%), 12 (20.7%) were inpatient based (hospital/rehabilitation ward), 5 (8.6%) were in institutional care (nursing/care homes) and 7 (12.1%) were in other (mixed or outpatient) settings. One study reported results separately for community and institutional settings and is counted in both settings. Simplified Nutritional Appetite Questionnaire (SNAQ Simplified, *n* = 14) and subject-reported appetite questions (*n* = 11) were the most common methods used to assess anorexia/appetite loss, but substantial variability in assessment tools was observed across studies. The most commonly reported outcomes were malnutrition and mortality. Malnutrition was assessed in 15 studies, with all reporting a significantly higher risk of malnutrition in older individuals with anorexia/appetite loss (vs. without) regardless of country or healthcare setting (community *n* = 9, inpatient *n* = 2, institutional *n* = 3, other *n* = 2). Of 18 longitudinal studies that assessed mortality risk, 17 (94%) reported a significant association between anorexia/appetite loss and mortality regardless of either healthcare setting (community *n* = 9, inpatient *n* = 6, institutional *n* = 2) or method used to assess anorexia/appetite loss. This association between anorexia/appetite loss and mortality was observed in cohorts with cancer (as expected) but was also observed in older populations with a range of comorbid conditions other than cancer. Overall, our findings demonstrate that, among individuals aged ≥ 65 years, anorexia/appetite loss is associated with increased risk of malnutrition, mortality and other negative outcomes across community, care home and hospital settings. Such associations warrant efforts to improve and standardize screening, detection, assessment and management of anorexia/appetite loss in older adults.

Keywords   anorexia; appetite loss; malnutrition; mortality; prevalence; systematic literature review

Introduction

Appetite loss is common among older adults and may occur as a symptom of underlying disease and/or as a side effect of medication use.[1] Appetite loss may also occur in the absence of any evident medical cause and be attributed to the aging process; this has been termed 'anorexia of aging'.[1,2]

Clinical and societal recognition of the burden of appetite loss in older adults is likely deficient for a variety of reasons. For example, there is no standardized approach to appetite assessment.[3] Similarly, there is no standardized terminology or definition for the condition, with terms such as appetite loss, anorexia of aging, unintentional weight loss, undernutrition and malnutrition used interchangeably across studies.[4] There is also a common assumption that appetite loss is a normal part of aging. These factors underpin variation in the reported prevalence of appetite loss, which ranges from 5% to 25% in community-dwelling older adults.[5–8] Prevalence is increased among nursing home residents and older hospitalized subjects, but the exact prevalence in these care settings is uncertain as appetite loss may go undetected, particularly if associated weight loss is minimal or absent.[3,9–11]

As such, there is a need to improve both the recognition and management of appetite loss among the growing population aged 65 years or older. To achieve these goals, however, a better understanding of the effects of appetite loss on morbidity, mortality and healthcare burden in older adults is required. The objective of this systematic literature review (SLR), therefore, was to characterize the relationship between appetite loss and negative outcomes in populations aged ≥ 65 years.

Methods

Study design and data sources

This SLR was conducted across PubMed, Embase®, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL) using a standardized methodical approach following guidance presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[12] The review is registered on PROSPERO under the identifier CRD42021270876. For the purposes of this SLR, the term 'anorexia/appetite loss' incorporated the following terms: anorexia (but not anorexia nervosa), loss or lack of appetite, appetite loss, decreased or reduced appetite, poor appetite or hyporexia (defined as a pathologically decreased appetite).

Search strategy: Inclusion/exclusion criteria

The full search strategies for each of the databases is given in Table S1. Inclusion criteria targeted studies in adults aged ≥ 65 years old with anorexia/appetite loss or at risk of anorexia, with a sample size of ≥ 20. Observational and real-world studies, economic models and interventional studies published in English language from 1 January 2011 to 31 July 2021 were eligible for inclusion. Studies in populations aged < 65 years, in a mixed age population that did not report separate results for those aged ≥ 65 years or in subjects with anorexia nervosa were excluded. Similarly, preclinical studies, clinical trials in healthy populations, case studies, notes/commentaries/editorials/opinions, congress abstracts or meta-analyses/reviews were not eligible for inclusion.

A rigorous, two-stage screening process was carried out independently by two reviewers (C. R. and K. S.). Stage 1 involved screening titles and abstracts based on inclusion/exclusion criteria; Stage 2 involved full-text screening of publications included at Stage 1 (title and abstract) review, including any for which there was a discrepancy between the two reviewers. Reference lists were also screened to identify any additional literature for further review. Reasons for exclusion were cross-checked between the two reviewers. The inclusion/exclusion agreement rate between the two reviewers was 90.5% for Stage 1 and 79% for Stage 2. Discrepancies were resolved by discussion to achieve agreement. Identification of papers and reasons for exclusion are presented in Figure 1.

Outcomes of interest included, but were not limited to, mortality, malnutrition, disability, health-related quality of life and healthcare resource utilization (Table 1). For the purpose of this paper, subjects were categorized into four healthcare setting cohorts: community-dwelling (independent living, free living in the community); inpatient (hospitalized, staying in a hospital or rehabilitation ward at the time of evaluation); institutional care (nursing care facility or geriatric day home); or other (mixed settings or settings not covered in previous categories).

Data extraction and quality assessment

Full publications of retained records were examined in detail for information relating to study size and location, subject characteristics and demographics of interest, healthcare setting, and outcomes of interest, according to population, interventions, comparator, outcomes, and study design (PICOS) criteria. Information on prevalence of anorexia and presence of key comorbidities including cognitive impairment, cancer or heart failure was also captured. Details of the instrument used to assess or screen for anorexia/appetite loss were recorded.

For observational longitudinal or prospective studies, quality/risk of bias was assessed using the Newcastle-Ottawa Scale (NOS).[13] The quality of observational cross-sectional studies was assessed using the modified NOS.[14] All studies ex-
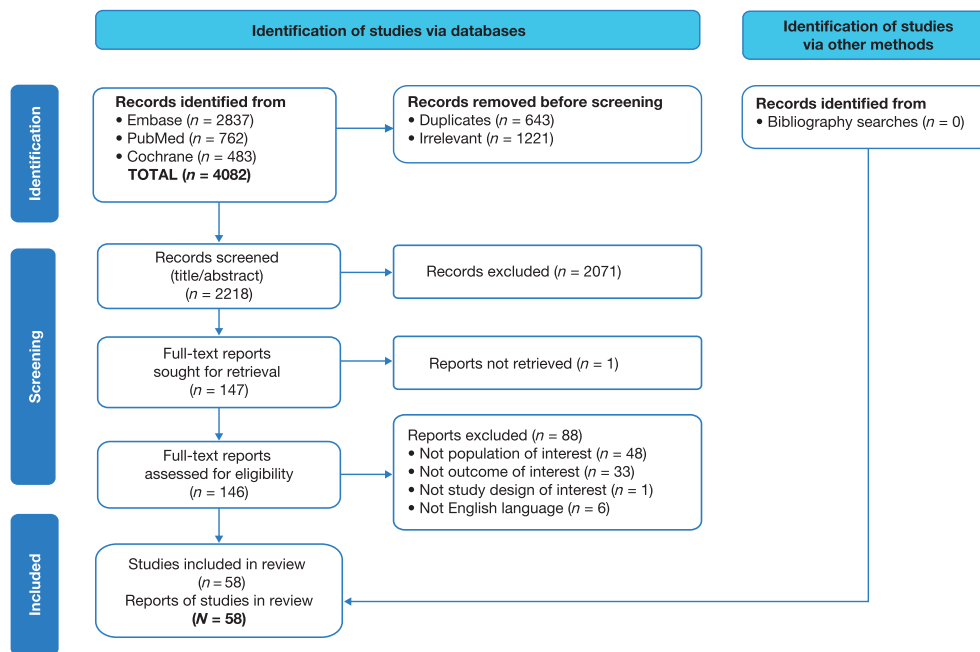
Figure 1 PRISMA flow diagram. Publications were identified from searches of Embase, PubMed and Cochrane databases. Duplicate entries or irrelevant types of publications (e.g., editorials, letters, reviews, congress abstracts, case reports, animal studies and paediatric studies) were removed initially before screening.

Table 1 Outcomes and healthcare setting cohorts assessed in the systematic literature review

Outcomes	Healthcare setting cohorts
Mortality, malnutrition, sarcopenia, functional status, increased care, hospitalization, falls, health-related quality of life, cognition, depression, disability, frailty, general health, infection, major adverse cardiovascular or cerebrovascular events, sleep quality, stroke, treatment (chemotherapy) interruption, weight loss	• Community-dwelling (independent living, free living in the community) • Inpatient (hospitalized, staying in a hospital or rehabilitation ward) • Institutional care (nursing care facility or care home) • Other (settings not included in previous categories such as mixed settings, unspecified settings and outpatient settings)

cept one[15] had either low or medium risk of bias, as detailed in *Table S2*.

Results

Study selection

Overall, 4082 unique citations were identified from the systematic searches of the three literature databases; 2218 passed through first screen (title/abstract), and 146 articles were retained for full-text review. In total, 58 publications meeting pre-defined criteria were included in the SLR (*Figure 1*).

Study characteristics

All 58 studies were observational studies, of which 60% (*n* = 35) were longitudinal and 40% (*n* = 23) were cross-sectional in design (*Table 2*). Sample sizes ranged widely, from ≤ 100 subjects to 1 466 598 for longitudinal[16] and to 13 151 for cross-sectional[55] studies. Most studies were conducted in Europe (*n* = 34; 58.6%) or Asia (*n* = 16; 27.6%) and only a few were carried out in the United States (*n* = 3; 5.2%), Australia (*n* = 2; 3.4%), the Middle East (*n* = 2; 3.4%) or Canada (*n* = 1; 1.7%). More than half of all studies were carried out in the community setting (*n* = 35; 60.3%), with the remainder carried out in inpatient (*n* = 12; 20.7%), institutional care (*n* = 5; 8.6%) or other (*n* = 7; 12.1% [outpatient *n* = 4; mixed *n* = 3]) settings. One study was conducted in community and institutional settings and

Table 2 Design and subject characteristics of studies identified during the systematic literature review (n = 58)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/ loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
			Longitudinal studies			
Hippisley-Cox and Coupland; 2017; UK (England)[16]	Prospective; N = 1 466 598; 1 Jan 2012 to 30 Sep 2016	Not reported but appears to be community-dwelling; all subjects aged ≥ 65 years, mean (SD) age = 75.3 (8.0) years; 54.9% female	Mean (SD) BMI = 27.3 (4.9)	In healthcare record; defined as the subject visiting a general practitioner for loss of appetite in the previous 12 months.	0.20%	Mortality
Cai et al.; 2020; UK (England)[17]	Retrospective; N = 4243; 1 Jan 2008 to 31 Mar 2017	Community-dwelling adults with depression; aged ≥ 65 years, mean (SD) age = 77.0 (7.9) years; 61.2% female	BMI not reported	In healthcare record; anorexia/loss of appetite criteria not defined.	54.8%	Mortality
Landi et al.; 2012; Italy[18]	Prospective; N = 2787; 1998 to 2000	Community-dwelling and receiving in-home care; all subjects aged ≥ 65 years, mean (SD) age = 80.4 (7.5) years; 60% female	BMI not reported	Food consumption (staff assessed); defined as staff responding yes to the question, 'In at least 4 of the last 7 days, the client ate one or fewer meals a day,' or 'In the last 3 days, noticeable decrease in the amount of food client usually eats.'	26.7%	Mortality
Huang et al.; 2014; Taiwan[19]	Retrospective; N = 1856; 1999 to 2000 with survivorship ascertained from the death registry until 31 Dec 2008	Community-dwelling; all subjects aged ≥ 65 years, mean (SE) age = 74.3 (0.3) years; 47.7% female	Mean (SE) BMI = 23.6 (0.2) Category: < 18.5 = 7.1% 18.5–23.9 = 48.2% 24.0–26.9 = 27.7% ≥ 27.0 = 17.0%	Appetite question (subject-reported); defined as subject responding 'poor' to the question, 'How is your current appetite?' Other possible responses included 'good' or 'fair'.	7.6%	Mortality
Huang et al.; 2018; Taiwan[20]	Retrospective; Male n = 970, female n = 967; 1999 to 2000 with survivorship ascertained from the death registry until 31 Dec 2008	Community-dwelling; age not reported; 49.9% female	Category: Male: < 18.5 = 4.4% 18.5–23.9 = 65.4% 24.0–26.9 = 20.9% ≥ 27.0 = 9.2% Female: < 18.5: 4.3% 18.5–23.9 = 49.1% 24.0–26.9 = 31.4% ≥ 27.0 = 15.2%	MNA-SF Q1 (food intake question); defined as subject responding 'poor' to the question, 'How is your current appetite?' Other possible responses included 'good' or 'fair'.	Male = 7.5% Female = 12.4%	Mortality
St John and Montgomery; 2014; Canada[21]	Prospective; N = 1751; baseline: 1991 to 1992, follow-up: 1996 to 1997	Community-dwelling; all subjects aged ≥ 65 years, mean (SD) age = 77.5 (7.1) years; 58% female	BMI not reported	CES-D; defined as subject responding 'some or little of the time (1–2 days)', 'occasionally or moderate amount of time (3–4 days)'	18%	Mortality

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Wijnhoven et al.; 2012; the Netherlands[22]	Retrospective; N = 1687; LASA 1: 1992 to 2007	Community-dwelling; LASA cohort, mean (SD) age = 74.5 (5.8) years; 50.4% female	Mean (SD) BMI = 26.7 (4.1)	CES-D; defined as subject responding 'some or little of the time (1–2 days)', 'occasionally or moderate amount of time (3–4 days)' or 'most of time (5–6 days)' to the question, 'I did not feel like eating, my appetite was poor,' in the past week. Other possible responses included 'rarely or none of time (< 1 day)'.	13.1%	Mortality
Fournier et al.; 2016; France[23]	Prospective; N = 156 (152 with appetite loss data); Mar 2003 to Sep 2006	Not reported but appears to be community-dwelling; age range, n (%): 65–74 years = 83 (53.2) ≥ 75 years = 73 (46.8); 48.7% female	BMI not reported	EORTC QLQ-C30; defined as a deterioration (from baseline) of > 10 points in appetite score on a scale from 0 to 100.	3 months = 16.7% 6 months = 13.7%	Mortality
Engelheart et al.; 2021; Sweden[24]	Prospective; N = 69; 2014 to 2017	Community-dwelling; all subjects aged ≥ 65 years, mean (range) age = 81.9 (65–97) years; 64% female	Mean [range] BMI = 26.8 [16–50], n = 61	Appetite question (subject-reported) with a visual analogue scale from 0 (*much reduced appetite*) to 10 (*very good appetite*); criteria for anorexia/loss of appetite not defined.	Prevalence of anorexia or appetite loss not reported	Mortality
Cox et al.; 2020; UK (England)[25]	Retrospective; N = 296; 2014 and 2017	Inpatient; all subjects aged ≥ 70 years, mean (SD) age = 82.7 (6.9) years; 43% female	Median (IQR) BMI = 25 (21, 28)	SNAQ Simplified; defined as score < 14.	41%	Mortality
Pilgrim et al.; 2016; UK (England)[26]	Prospective; N = 178; dates not reported	Inpatient (geriatric ward); all subjects described as 'older', mean (SD) age = 86.6 (4.7) years; 100% female	Mean (SD) BMI = 24.8 (1.3), n = 172	SNAQ Simplified; defined as score < 14.	Admission = 42%, 6-month follow-up = 38%	Mortality Infection Increased care Weight loss Sarcopenia Hospitalization
Hofer et al.; 2018;	Prospective; N = 149;	Inpatient;	BMI not reported	EORTC QLQ-C30; defined as no appetite loss (score of	Mild appetite loss = 30%	Mortality

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/ loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Austria[27]	Jan 2009 to Apr 2016	all subjects aged > 67 years, mean [range] age = 77.8 [67.1–95.3] years; 46% female		0), mild loss (score of 1–66) and moderate to severe loss (score of 67–100) on a 100-point numeric rating scale for appetite question.	Moderate to severe appetite loss = 13%	Mortality MACCE Stroke Hospitalization
Taniguchi et al.; 2019;[28] Japan	Retrospective; N = 139; TAVI received Jul 2014 and Oct 2018, follow-up: max of 2 years	Inpatient followed by community or institution upon discharge, all subjects underwent TAVI; mean (SD) age = 83.6 (5.2) years; 63.3% female	Mean (SD) BMI = 22.4 (4.0)	Food consumption (staff-assessed); assessed averaged intake rate for breakfast, lunch and dinner on the day just before discharge. The good appetite group was defined as having a dietary intake rate > 90% just before discharge, whereas the less appetite group was defined as a dietary intake rate ≥ 90%.	24.5%	
Rawle et al.; 2020;[29] UK	Retrospective; N = 134; Community-dwelling n = 70, care (nursing) home n = 64; 10 Mar to 8 Apr 2020	Inpatients hospitalized with COVID-19 (with subgroups of subjects previously residing in community or care [nursing] home); all subjects aged ≥ 80 years, median (IQR) age, years: Total = 86 (7.6), community = 85 (6), care home = 88.5 (7), P < 0.001; % female: Total = 45.5%, community = 44.3%, care home = 46.9%	BMI not reported	Mentioned in health record; defined as being present in the health record.	Total = 21.2% Community = 15.7% Care home (nursing) = 28.1%	Mortality
Schmidt et al.; 2014;[30] Germany	Prospective; N = 126; Jun 2008 to Jul 2010	Inpatients scheduled for surgery for gastrointestinal, genitourinary or gynaecological cancer; all subjects aged ≥ 65 years, mean (SD) age = 72 (5.6) years; 55.6% female	Mean (SD) BMI = 26.7 (4.9)	EORTC QLQ-C30; anorexia/ appetite loss criteria not defined.	Prevalence not reported	Mortality
Landi et al.; 2013;[8] Italy	Prospective; N = 1904; Enrolment: Feb to Dec 2005, follow-up: 12 months (Dec 2006)	Institution (nursing home); all subjects aged ≥ 65 years, mean (SD) age = 83.5 (8.1) years; 71.6% female	BMI not reported	Food consumption (staff-assessed); defined as staff answering 'yes' to the question, 'In at least 4 of the last 7 days, the client	12.6%	Mortality

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/ loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Mikami et al.; 2019; Japan[31]	Prospective; N = 316; Jan 2014 to Jan 2015	Institution (nursing home); all subjects described as 'elderly', mean (SD) age = 84.9 (8.3) years; 81% female	Mean (SD) BMI = 21 (3.5)	ate one or fewer meals a day.'	Prevalence of anorexia or poor appetite not reported	Mortality
Kanamori et al.; 2012; Japan[32]	Prospective; N = 72; 2000 to 2003	Other (outpatients receiving haemodialysis, ≥ 65 years subset); mean (SD) age = 71.8 (5.6) years; 41.7% female	BMI not reported	CNAQ, SNAQ Simplified; defined as CNAQ total scores ≤ 28 (poor appetite) and > 28 (good appetite). SNAQ criteria not defined.	Prevalence of anorexia or poor appetite not reported	Mortality
de Almeida Mello et al.; 2020; Belgium[33]	Retrospective; N = 6334; dates not reported	Community-dwelling; all subjects aged ≥ 65 years, mean (SD) age = 80.6 (6.9) years; 70.6% female	BMI not reported	Appetite question (subject-reported) based on a 100-mm visual analogue scale; appears to be defined as scores ≤ 74 (less appetite) and ≥ 75 (more appetite).	Prevalence of anorexia or poor appetite not reported	Malnutrition
Schilp et al.; 2011; the Netherlands[34]	Prospective; N = 1120; 1992 to 1993	Community-dwelling; all subjects aged ≥ 65 years, mean (SD) age = 74.1 (5.7) years; 51.5% female	Mean (SD) BMI = 27.2 (3.9)	Appetite assessment method not reported.	Prevalence of anorexia or poor appetite not reported	Malnutrition
Lambert et al.; 2017; Germany[15]	Prospective; N = 317; Enrolment: June 2014 to June 2015, follow-up: Length not reported	Inpatient (followed by community or nursing home on discharge); subset of subjects aged ≥ 70 years hospitalized ≥ 2 nights; % female not reported	BMI not reported for the ≥ 70-year-old subset	CES-D; defined as subject responding 'some or little of the time (1–2 days)', 'occasionally or moderate amount of time (3–4 days)' or 'most of time (5–6 days)' to the question, 'I did not feel like eating, my appetite was poor,' in the past week. Other possible responses included 'rarely or none of time (< 1 day)'.	10.9%	Malnutrition
Cox et al.; 2021; UK (England)[35]	Prospective; N = 204; SNAQ measure: 5 Mar to 30 Apr 2019, sarcopenia measures: 2006 to 2018	Community-dwelling: Case (SNAQ < 14) n = 102, control (SNAQ > 14) n = 102, all subjects aged ≥ 65 years, mean (SD) age, years:	Mean (SD) BMI: Case = 25.6 (5.1) Control = 25.8 (4.1)	Appetite assessment method not reported; anorexia/loss of appetite criteria not defined. SNAQ Simplified; defined as score < 14.	Prevalence of anorexia or poor appetite not reported	Sarcopenia

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Senoo et al.; 2020; Japan[36]	Prospective; N = 173; baseline: 2015, follow-up: 2016 to 2018	Case = 68.0 (5.7), control = 67.6 (5.4); % female: Case = 95.1%, control = 95.1%	BMI category, n (%) < 18.5 = 7 (4.1)	SNAQ Simplified; defined as score ≤ 14.	32.9%	Sarcopenia
Tsutsumimoto et al.; 2018; Japan[7]	Prospective; N = 4393; dates not reported	Community-dwelling; all subjects aged ≥ 75 years, median (IQR) age = 80 (78–83) years; 64.7% female	Mean (SD) BMI = 22.9 (3.0)	SNAQ Simplified; defined as score ≤ 13.	10.7%	Disability
Martinez-Reig et al.; 2014; Spain[37]	Prospective; N = 678; 2007 to 2009	Community-dwelling; all subjects aged ≥ 70 years, mean (SD) age = 78.0 (5.7) years; 57.8% female	Mean (SD) BMI = 29.3 (4.8)	MNA-SF Q1 (food intake question); criteria for anorexia/loss of appetite not defined.	Severe decrease in food intake = 0.4% Moderate decrease = 15.2%	Disability
Hsu et al.; 2019; Taiwan[38]	Retrospective; N = 1986; 1999 to 2003	Community-dwelling; all subjects aged ≥ 70 years, mean (SD) age = 75.8 (4.9) years; 44.5% female	Mean (SD) BMI = 22.9 (3.4)	CES-D; authors combined the two 'no and seldom' responses of the CES-D into 'no', poor appetite loss and the two 'often and usually' responses into 'yes' poor appetite.	Prevalence of anorexia or appetite loss not reported	Increased care
Salminen et al.; 2018; Finland[39]	Prospective; N = 1032; 1920 birth cohort, data collected Jan 1991	Community-dwelling; all subjects aged ≥ 70 years, mean age = 70 years; 64% female	BMI category, n (%): < 25 = 297 (38), 25.0–29.9 = 354 (45), ≥ 30 = 134 (17)	Appetite question (subject-reported); defined as subject responding 'sometimes or daily' to lack of appetite question. Other possible responses included 'never'.	10%	Increased care
Sheppard et al.; 2013; USA[40]	Prospective; admission to nursing home: Yes n = 75, no n = 924; baseline: Nov 1999 to Feb 2001, follow-up: 8.5 years	Community-dwelling; all subjects aged ≥ 65 years, mean (SD) age, years: Yes nursing home admission = 79.4 (7.2), no nursing home admission = 74.9 (6.6), P < 0.001; % female: Yes nursing home admission = 56%, no nursing home admission = 49.3%	BMI not reported	PROMIS; defined as subjects responding 'fair' or 'poor' to the question, 'Would you say your appetite is usually very good, good, fair or poor?'	Yes nursing home = 29.3% No nursing home = 16.2%	Increased care

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/ loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Salanitro et al.; 2012; USA[41]	Prospective; N = 980; Dec 1999 to Feb 2001	Community-dwelling; all subjects aged ≥ 65 years, mean (SD) age = 75.3 (6.7) years; 49.5% female	BMI category, n (%): < 18.5 = 21 (2.1) 18.5–25 = 288 (29.4) 25–30 = 369 (37.7) 30–35 = 199 (20.3) 35 + = 103 (10.5)	Appetite question (subject-reported); defined as subject responding 'fair' or 'poor' to the question, 'Would you say your appetite is usually very good, good, fair or poor?'	16.9%	Hospitalization
Van Dronkelaar et al.; 2019; the Netherlands[42]	Prospective; N = 400; Oct 2015 to Feb 2017	Inpatient (acute inpatients); all subjects aged ≥ 70 years, mean (SD) age = 80.1 (6.7) years; 48.5% female	Median (IQR) BMI = 24.5 (21.9–28.6)	SNAQ Short AL question; defined as subject responding 'yes' to the question, 'Have you experienced a decreased appetite over the last month?' at hospital admission or to the question, 'Have you experienced a decreased appetite since hospital admission?' for discharge and post-discharge assessments.	50.5% at hospital admission 34.0% at discharge 27.8% at 1-month post-discharge 17.0% at 3-month post-discharge	Sarcopenia
Dent et al.; 2015; Australia[43]	Prospective; N = 172; 22 Oct 2010 to 23 Dec 2011	Inpatient; all subjects aged ≥ 70 years, mean (SD) = 85.2 (6.4) years; 72% female	BMI category, n (%): < 22 = 58 (34) 22–30 = 75 (44) > 30 = 39 (23)	SNAQ Simplified; defined as score ≤ 14.	63%	Functional status Increased care Hospitalization
Mendelson et al.; 2018; Israel[44]	Retrospective; N = 107: FIM > 70 n = 56, FIM ≥ 90 n = 37; Feb to Jul 2014	Inpatient (rehab centre); all subjects with hip fracture, FIM > 70: mean (SD) age = 78.7 (7.0) years; 71.4% female	BMI not reported	SNAQ Short AL question; defined as subject responding 'yes' to the question, 'Have you experienced a decreased appetite over the last month?'	FIM ≥ 90 = 40.5% FIM < 90 (and > 70) = 68.4% P = 0.048	Functional status
Van Grootven et al.; 2020; Belgium[45]	Prospective; N = 189; Sep 2016 to Jun 2017	Inpatient; all subjects aged ≥ 75 years, mean (SD) age = 84 (5) years; 47% female	BMI not reported	Appetite question (subject-reported); defined as self-reported loss of appetite in the past 3 months.	40%	Functional status
Kirkhus et al.; 2019; Norway[46]	Prospective; N = 288; Jan 2013 to Apr 2015	Other (outpatient with cancer aged ≥ 70 years); mean (SD) age = 76.9 (5.1) years; 44% female	BMI not reported	EORTC QLQ-C30; anorexia/ appetite loss criteria not defined.	Prevalence of anorexia or appetite loss not reported	Functional status HRQoL
Won et al.; 2019;	Prospective; N = 75;	Other (outpatient);	BMI category, n (%): < 23 = 43 (57.3)			Treatment interruption (Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Korea[47]	Apr 2012 to Nov 2013	mean (SD) = 72.7 (5.0) years; 36% female	≥ 23 = 32 (42.7)	EORTC QLQ-C30; anorexia/appetite loss criteria not defined.	Prevalence of anorexia or appetite loss not reported	Malnutrition
			Cross-sectional			
Kiesswetter et al.; 2020; Germany[48]	Cross-sectional; community-dwelling: N = 1073 2009; Geriatric day hospital: N = 180 2012; Home care: N = 335 2010; Nursing home: N = 197 2007	Multiple settings, but reports reported separately for each: Community-dwelling, geriatric day hospital, home care and nursing home with results reported separately for each; mean (SD) age: Community = 76 (6.6); Geriatric day hospital = 79.3 (6.2); Home care = 80.9 (7.7); Nursing home = 85.5 (7.9); % female: Community = 50.2%; Geriatric day hospital = 71.7%; Home care = 63.6%; Nursing home = 73.6%	BMI not reported	Appetite question (subject-reported); anorexia/appetite loss criteria not defined.	Community = 9.5%; Geriatric day hospital = 25.6%; Home care = 37.3%; Nursing home = 35.4%	Malnutrition
Hirose et al.; 2014; Japan[49]	Cross-sectional; N = 1098 Malnourished n = 235 Risk of malnutrition n = 596 Well-nourished n = 267; 1 May 2009 to 30 Nov 2009	Other (mixed community-dwelling or nursing home); mean (SD) age, years: Malnourished = 84.6 (8.2); Risk of malnutrition = 83.8 (8.1); Well-nourished = 81.0 (7.5); % female: Malnourished = 74.5%; Risk of malnutrition = 72.7%; Well-nourished = 62.2%	BMI not reported	MNA-SF Q1 (food intake question): defined as subject self-reported appetite loss or reduced food intake not attributable to specific reasons.	26.6%	Malnutrition
Pohlhausen et al.; 2016; Germany[50]	Cross-sectional; N = 353: Female n = 225, male n = 128; 2010	Community-dwelling (receiving home care); all subjects aged > 64 years, mean (SD) age: Female = 82.0 (7.5) years, male = 79.1 (7.8) years; 63.7% female	Mean (SD) BMI: Female = 28.2 (6.5) Male = 28.3 (5.7)	Appetite question (subject-reported); defined as subjects responding 'poor' to the question asking them to rank their appetite. Other possible responses	Female = 3.1% Male = 5.5%	Malnutrition

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
van der Pols-Vijlbrief et al.; 2016; the Netherlands[51]	Cross-sectional; N = 300; dates not reported	Community-dwelling, (receiving home care); all subjects aged ≥ 65 years, mean (SD) age = 81.7 (7.6); 68.3% female	Mean (SD) BMI = 25.8 (5.2)	SNAQ[65+] Simplified 4-items; appetite anorexia/loss of criteria not defined. included 'very good', 'good' or 'moderate'.	21.3%	Malnutrition
Nambooze et al.; 2014; Laos[52]	Cross-sectional; 3 ethnic groups (N = 144): Oy n = 53, Brau n = 41, Lao n = 50; 2012 and 2013	Community-dwelling; all subjects aged ≥ 65 years, age range by ethnic group, n (%): Oy: 65–74 = 25 (47.2) 75–84 = 19 (35.8) > 85 = 9 (17.0) Brau: 65–74 = 28 (68.3) 75–84 = 8 (19.5) > 85 = 5 (12.2) Lao: 65–74 = 30 (60.0) 75–84 = 13 (26.0) > 85 = 7 (14.0); % female: Oy = 54.7%, Brau = 61%, Lao = 70%	BMI category: n (%): Oy < 21 = 49 (92.5) ≥ 21 = 4 (7.5) Brau < 21 = 37 (90.2) ≥ 21 = 4 (9.8) Lao < 21 = 29 (58.0) ≥ 21 = 21 (42.0)	MNA Q1 (food intake question); anorexia/loss of appetite criteria not defined.	Prevalence of anorexia or appetite loss not reported	Malnutrition
Buhl et al.; 2021; Denmark[53]	Cross-sectional; N = 126: Normal protein intake ≥ 1.0 g/kg/day (n = 58), low protein intake ≤ 1.0 g/kg/day (n = 68); Jan 2017 to Aug 2018	Community-dwelling; all subjects aged ≥ 80 years, mean (SD) age = 86 (3.6) years; 63.5% female	Median [95% CI] BMI: Normal protein intake = 25.1 [24.1, 26.1] Low protein intake = 27.4 [26.5, 28.4]	SNAQ Simplified; score ≤ 14.	Normal protein intake = 3.4% (0.8, 13.1) Low protein intake = 10.3% (4.9, 20.3)	Malnutrition
Berggren et al.; 2020; Sweden[54]	Cross-sectional; N = 121; 2011 and 2012	Community-dwelling, receiving home care; mean [95% CI] age = 83.5 [82.3, 84.7] years; 67.8% female	Median [95% CI] BMI = 23.3 [22.6, 24.7]	ESAS Q7 and FAACT Q1; anorexia/appetite loss criteria not defined.	Prevalence of anorexia or appetite loss not reported	Malnutrition
Arkkukangas et al.; 2020; Sweden[55]	Cross-sectional; N = 13 151: 12 290 with fall data, 3385 with fall and appetite data (all female); 2017	Other (mixed community-dwelling or nursing home [4%]); all subjects aged ≥ 70 years, age range, n (%): 70–74 = 4858 (36.9) 75–79 = 3296 (25.1) 80–84 = 1942 (14.8) 85–89 = 2041 (15.5) 90 + = 1014 (7.7);	BMI not reported	Appetite question (subject-reported); anorexia/loss of appetite criteria not defined.	Women with falls in the past 12 months = 6.6%	Falls

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Tsutsumimoto et al.; 2020; Japan[56]	Cross-sectional; N = 9496; Nagoya: Jul 2013 to Dec 2013, Obu: Feb 2015 to Aug 2016	Community-dwelling; all subjects aged ≥ 65 years, mean (SD) age = 74.1 (5.4) years; 48.6% female	BMI not reported	SNAQ Simplified; defined as score ≤ 13.	9.8%	Sarcopenia
Tsutsumimoto et al.; 2017; Japan[57]	Cross-sectional; N = 4417; dates not reported	Community-dwelling; all subjects aged ≥ 70 years, mean (SD) age = 75.8 (4.3) years; 53% female	Mean (SD) BMI = 22.9 (3.0)	SNAQ Simplified; defined as score ≤ 13.	Total = 10.6% Non-frail = 7.9% Pre-frail: 14.8% Frail: 21.2%, P < 0.001	Frailty
Pisu et al.; 2018; USA[58]	Cross-sectional; N = 1457; Nov 2013 to Jun 2015	Community-dwelling with cancer; all subjects aged ≥ 65 years, mean (SD) age = 74.2 (5.8) [65–99] [range] years; 52.7% female	Mean (SD) BMI = 27.1 (5.1)	MDASI; anorexia/loss of appetite criteria not defined.	Prevalence of anorexia or appetite loss not reported	HRQoL
Yamamoto et al.; 2020; Japan[59]	Cross-sectional; N = 1042; Oct to Dec 2016	Community-dwelling; mean (SD) age = 77.5 (4.9) years; 59.8% female	Mean (SD) BMI = 23.2 (10.7)	CNAQ; anorexia/loss of appetite criteria not defined.	Prevalence of anorexia or appetite loss not reported	Sleep quality
Kim et al.; 2019; Japan[60]	Cross-sectional; normal n = 822: Physical frailty n = 30, mild cognitive impairment n = 314, cognitive frailty n = 25; 2016	Community-dwelling; mean (SD) age, years: Normal = 76.6 (4.5), physical frailty = 80.9 (5.3), mild cognitive impairment = 77.8 (4.7), cognitive frailty = 82.3 (6.6); % female: Normal = 61.5%, physical frailty = 46.7%, mild cognitive impairment = 56.2%, cognitive frailty = 64%	Mean (SD) BMI: Normal = 22.9 (3.2) Physical frailty = 22.8 (4.0) Mild cognitive impairment = 23.4 (3.1) Cognitive frailty = 21.5 (3.8)	CNAQ; anorexia/loss of appetite criteria not defined.	Prevalence of anorexia or appetite loss not reported	Cognition Falls
Donini et al.; 2011; Italy[61]	Cross-sectional; N = 527: With anorexia n = 112, without anorexia n = 415; Apr 2006 to Jun 2007	Other (mixed community-dwelling or nursing home, or rehabilitation/acute wards ≥ 65 years); mean (SD) age, years: With anorexia = 83.0 (7.0), without anorexia = 76.6 (8.0);	Mean (SD) BMI: With anorexia = 22.6 (5.0) Without anorexia = 26.7 (4.0) P < 0.05	Food consumption (staff-assessed); defined as a ≥ 50% reduction in food intake versus a standard meal (over 3 days), in absence of oral disorders preventing mastication.	21.3%	Cognition Depression Functional status General health Increased care

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Fonad et al.; 2015; Sweden[62]	Cross-sectional; Fallers n = 434, non-fallers n = 759; Oct 2008 to Mar 2009	% female: With anorexia = 63.4%, without anorexia = 59.8% Community-dwelling; Age range: Fallers aged ≥ 75 years 75–84 years = 59.9% ≥ 85 years = 40.1% Non-fallers aged ≥ 75 years 75–84 years = 66.7% ≥ 85 years = 33.3%; % female: Fallers aged ≥ 75 years = 64%, non-fallers aged ≥ 75 years = 61%	BMI not reported	Appetite question (subject-reported); defined as answering 'yes' to the questions, 'Has your appetite decreased in the previous 6-month period?' or 'Has your food intake declined in the previous 6-month period?'	Fallers, n (%): Appetite decrease = 94 (22) Food intake decline = 108 (25) Non-fallers, n (%): Appetite decrease = 84 (11) Food intake decline = 90 (12)	Falls
Acar Tek and Karaçil-Ermumcu; 2018; Turkey[63]	Cross-sectional; N = 407; dates not reported	Community-dwelling; all subjects described as 'elders', mean (SD) age, years: Men = 72.8 (6.7), women = 71.1 (6.4); 65% female	Mean (SD) BMI: Men = 27.5 (4.3) Women = 29.8 (5.8)	SNAQ Simplified; defined as score ≤ 14.	28.7%	HRQoL
Landi et al.; 2013; Italy[64]	Cross-sectional; N = 354; dates not reported	Community-dwelling; mean (SD) age = 85.8 (4.9) years; 66.7% female	Mean (SD) BMI = 25.6 (4.5)	Food consumption and appetite questions (subject-reported); defined as answering 'yes' to the question, 'Is the amount of food intake decreased in the last year?' or 'poor' to the question, 'How is your appetite in general?' Other possible responses included 'normal' or 'good'.	20.6%	Sarcopenia
Reijnierse et al.; 2015; the Netherlands[65]	Cross-sectional; N = 185; Mar 2011 to Jan 2012	Community-dwelling (but all pts seen in geriatric outpatient clinic); mean (SD) age = 82.0 (7.3) years; 60% female	Mean (SD) BMI = 25.7 (4.4)	SNAQ Short AL question; anorexia/loss of appetite criteria not defined.	27.6%	Sarcopenia
Nakatsu et al.; 2015; Japan[66]	Cross-sectional; N = 84; Aug 2013 to Sep 2013	Community-dwelling; all subjects aged ≥ 65 years, mean (SD) age = 76.4 (9.3) years; 64% female	Mean (SD) BMI = 23.5 (3.2)	SNAQ Simplified; anorexia/ loss of appetite criteria not defined.	Prevalence of anorexia or appetite loss not reported	Depression Functional status
Dent et al.; 2018;	Cross-sectional[a]; N = 172;	Inpatient;	Mean (SD) BMI = 25.3 (6.5)	SNAQ Simplified; defined as score ≤ 14.	63%	Malnutrition

(Continues)

Table 2 (continued)

Author; year; country	Study design; sample size; study period	Study setting; age; percentage female	BMI, kg/m²	Anorexia or appetite assessment method; definition of anorexia/ loss of appetite	Prevalence of anorexia or poor appetite	Outcomes assessed
Australia[67]	Oct 2010 to Dec 2011	all subjects aged ≥ 70 years, mean (SD) age = 85.2 (6.4) years; 72% female				Malnutrition
Madeira et al.; 2018; Portugal[68]	Cross-sectional; N = 1186; Oct 2015 to Apr 2016	Institution (nursing home); all subjects aged ≥65 years, mean [95% CI] age = 83.4 [82.8, 83.7] years; 72.8% female	Mean [95% CI] BMI = 27.4 [27.0, 27.8]	Appetite question (subject-reported); anorexia/loss of appetite criteria not defined.	% [95% CI] on a scale from 1 = no appetite to 5 = lots of appetite: 1 = 5.8 [3.9, 8.6] 2 = 18.4 [15.9, 21.2] 3 = 42.7 [38.5, 46.9] 4 = 22.6 [19.0, 26.6] 5 = 10.5 [8.3, 13.3]	Malnutrition
Donini et al.; 2013; Italy[9]	Cross-sectional; N = 100; Jan to Jun 2005	Institution (nursing home); mean (SD) age = 80.2 (10) years; 71% female	BMI category, %: Male: < 18.5 = 0% 18.5–24.9 = 50% 25–29.9 = 25% ≥ 30 = 25% Female: < 18.5 = 6.7 18.5–24.9 = 30 25–29.9 = 26.7 ≥ 30 = 36.6 Mean (SD) BMI by MNA nutritional status: Normal = 32.6 (6) At risk = 26.9 (5) Malnutrition = 19.3 (1) $P = 0.00$	Food consumption (staff-assessed); anorexia/loss of appetite criteria not defined.	Subjects (%) with decreased, scarce or absent appetite: Normal nutrition status = 16.7% At-risk status = 54.4% Malnutrition status = 61%	Malnutrition
van Steijn et al.; 2014; the Netherlands[69]	Cross-sectional; N = 102; Nov 2010 to Feb 2011	Other (outpatients with Parkinson's disease); mean (SD) age = 76.4 (6.3) years; 47.1% female	Mean (SD) BMI = 25.2 (3.6)	CNAQ; anorexia/loss of appetite criteria not defined.	Prevalence of anorexia or appetite loss not reported	Malnutrition

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; CNAQ, Council on Nutrition Appetite Questionnaire; COPD, chronic obstructive pulmonary disease; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; ESAS, Edmonton Symptom Assessment System; FAACT, Functional Assessment of Anorexia/Cachexia Treatment; FIM, Functional Independence Measure; FRAIL, Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight; GDS, Geriatric Depression Scale; IQR, interquartile range; LASA, Longitudinal Aging Study Amsterdam; MDASI, MD Anderson Symptom Inventory; MNA, Mini Nutritional Assessment; MNA-SF, Mini Nutritional Assessment-Short Form; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; SE, standard error; SNAQ Short, Short Nutritional Assessment Questionnaire; SNAQ Simplified, Simplified Nutritional Appetite Questionnaire; TAVI, transcatheter aortic valve implantation.
aDent (2018) is the same study population as Dent (2015). Although both were prospective longitudinal studies, Dent (2018) is classified here as cross-sectional because the outcome of interest for the systematic literature review (malnutrition) was assessed at the same time point as appetite (at hospital admission), whereas outcomes in Dent (2015) were assessed at discharge.

reported results separately for each.[48] This study, therefore, is counted in both the community and institutional settings throughout the manuscript.

By design, all subjects were aged $\geq$ 65 years. Twenty-three studies reported a mean or median age > 80 years (*Table 2*). Cohorts were predominantly female. Mean body mass index (BMI) at study entry ranged between 21.0 and 29.3 kg/m^2.[31,37] Six studies were in subjects with active cancer or a history of cancer[23,27,30,46,47,58]; two studies were in subjects hospitalized for a fracture[44] or other trauma[15]; and one study each was in subjects with Parkinson's disease,[69] subjects receiving haemodialysis[32] or subjects hospitalized for COVID-19.[29] The remaining studies were not specific to a given health condition (*Table 2*).

Assessment of anorexia/appetite loss

Methods used to assess anorexia/appetite loss were reported in nearly all (*n* = 57; 98.3%) studies (*Tables 2* and *S3*). The most commonly used assessment tool for appetite was the self-reported Simplified Nutritional Appetite Questionnaire (SNAQ Simplified, 14 studies)[70]; most of these studies employed a SNAQ Simplified score of $\leq$ 14 or $\leq$ 13 (in some studies) out of 20 as the threshold for defining anorexia/appetite loss. Four studies used the Mini Nutritional Assessment (MNA) or the Mini Nutritional Assessment Short Form (MNA-SF), three studies used the Short Nutritional Assessment Questionnaire (SNAQ Short),[71] three studies used the Council on Nutrition Appetite Questionnaire (CNAQ)[70] and one study used the Functional Assessment of Anorexia/Cachexia Treatment (FAACT).[72] The remaining studies used assessments of quality of life that included specific questions on appetite, subject- or staff-reported assessments of food intake and/or appetite, or history of loss of appetite taken from subject medical records (*Tables 2* and *S3*).

Prevalence of anorexia/appetite loss

Prevalence of anorexia/appetite loss was reported in 41 (70.7%) studies and ranged widely, from 0.20% in a study of 1 466 598 older UK residents (anorexia/appetite loss was derived from medical records and was defined as the patient visiting a general practitioner for loss of appetite in the previous 12 months)[16] to 63% in a study of hospitalized older subjects in South Australia (anorexia/appetite loss was derived from the SNAQ Simplified and defined as a score $\leq$ 14)[43] (*Table 2*). When estimated by residential setting, prevalence ranged from 0.20%[16] to 55%[17] in community-dwelling subjects, 5.8%[68] to 61%[9] among subjects in institutional care, 13%[27] to 63%[43] in inpatient settings and 6.6%[55] to 26.6%[65] in other settings (mixed and outpatient). The wide variation in reported prevalence across studies is explained, in part,

by heterogeneity with respect to populations assessed, study design and the methods used to evaluate or define anorexia/appetite loss.

Eleven studies with a reported prevalence defined anorexia/appetite loss as a SNAQ Simplified score of $\leq$ 14 or $\leq$ 13 (*Table 2*).[7,25,26,36,43,51,53,56,57,63,67] Among these 11 studies with a consistent definition, the prevalence of anorexia/appetite loss ranged from 3.4%[53] to 33%[36] for community-dwelling older adults (*n* = 7 studies) and from 38%[26] to 63%[43] in the inpatient care setting (*n* = 4 studies).

Relationship between anorexia/appetite loss and malnutrition

All 15 studies (3 longitudinal and 12 cross-sectional) that assessed the association of anorexia/appetite loss and malnutrition confirmed a higher risk of malnutrition in populations with anorexia/appetite loss (vs. without), regardless of country of origin, healthcare setting or measure of malnutrition (*Figure 2* and *Table S4*). Ten of the 15 studies reported odds ratios (ORs) (*Figure 3*). Measures of malnutrition included mostly the MNA (full and short forms) (*Table S4*) as well as measures of unintentional weight loss, BMI, upper arm and calf circumferences, and protein intake (*Table S4*).

Of the three longitudinal studies, two community-based studies concluded that anorexia/appetite loss was associated with a 76% increased risk[33] of unintentional weight loss and a 63% increased risk[34] of malnutrition (vs. those without anorexia/appetite loss) over a period of 1 and 9 years, respectively (*Figure 3* and *Table S4*). A third study of 317 orthopaedic subjects hospitalized for at least two nights reported that the likelihood of malnutrition was 4.5 times higher among those with anorexia/appetite loss than those without anorexia/appetite loss (OR [95% confidence interval, CI] = 4.54 [2.31, 8.90], $P < 0.001$)[15] (*Figure 3*).

The 12 cross-sectional studies assessed populations with different comorbidities and included a range of care settings (*Table S4*). Regardless of setting, a higher risk of malnutrition was reported in those with anorexia/poor appetite than in those without anorexia/appetite loss. The highest risk of malnutrition was reported from a multivariate analysis of 1098 Japanese individuals with anorexia/appetite loss living either in institutional care (nursing home) or within the community (OR [95% CI] = 16.45 [7.84, 34.54], $P < 0.001$)[49] (*Figure 3*). A study in the Netherlands reported that the odds of an unfavourable nutritional status increased by 18% for every point decrease of the CNAQ score (OR [95% CI] = 0.82 [0.70, 0.95], $P = 0.008$) in 102 older outpatients with Parkinson's disease.[69] In a separate study of 300 community-dwelling individuals receiving home care in the Netherlands, better appetite was significantly associated with lower risk of malnutrition (OR [95% CI] = 0.66 [0.58, 0.76], $P < 0.05$), for each point increase in SNAQ Simplified score.[51]
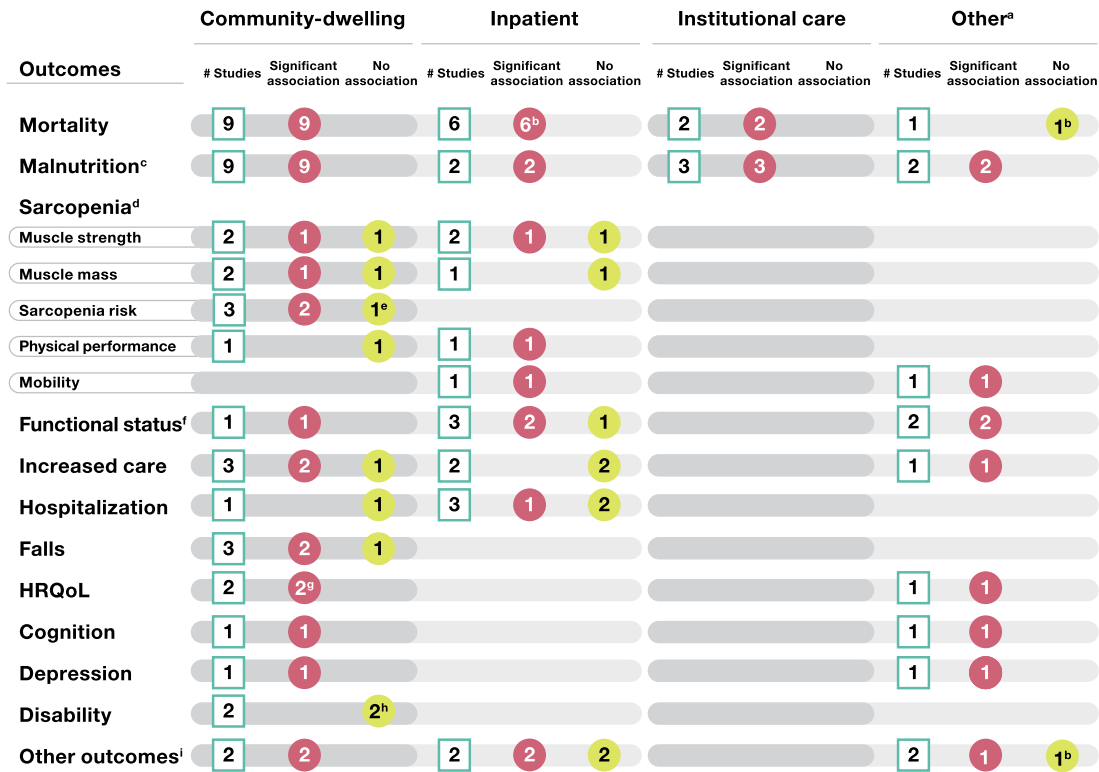
Figure 2 Summary of association between anorexia/appetite loss and outcomes in studies identified (*n* = 58 articles), shown by healthcare setting. White squares indicate the number of studies assessing the outcome; red circles indicate the number of studies where anorexia/appetite loss was associated with poor outcomes; and yellow circles indicate the number of studies where anorexia/appetite loss was not associated with the outcome. HRQoL, health-related quality of life. [a]'Other' includes studies with mixed settings (no separate results by setting) and studies where care was provided in an outpatient setting. [b]Based on findings from a univariate analysis, a significant association was found between anorexia/appetite loss and mortality in reference[27] but not in reference.[32] An association between anorexia/appetite loss and treatment interruption was found in univariate, but not multivariate, analysis.[47] [c]In Kiesswetter et al. (2020),[48] an association of appetite loss with malnutrition was reported separately for both community-dwelling and institutional care cohorts; therefore, this study has been counted in both the categories. [d]Sarcopenia was reported in seven studies. [e]Poor appetite alone was not significantly associated with sarcopenia development in participants with poor appetite and without low masticatory function; however, a significantly higher risk of sarcopenia was observed in those who had both poor appetite and low masticatory function.[36] [f]In Nakatsu et al. (2015),[66] the authors measured walking speed, chair stand time, hand-grip strength and timed 'Up and Go' test and characterized these outcomes as measures of physical performance and not sarcopenia; however, other studies also used these measures to assess sarcopenia. A significant correlation between walking speed, chair stand time and timed 'Up and Go' test and better appetite was noted, whereas the correlation between hand-grip strength and appetite was not statistically significant. [g]Lack of appetite was found to be associated with HRQoL as assessed by the Short Form-12 mental component summary score only, but not with the Short Form-12 physical component summary score.[58] [h]Anorexia was found to be associated with a significantly higher risk of disability in both studies in unadjusted or non-fully adjusted models, but this association was no longer significant in fully adjusted models.[7,37] [i]'Other outcomes' includes frailty, general health, infection, major adverse cardiovascular or cerebrovascular events, sleep quality, stroke, treatment (chemotherapy) interruption and weight loss, which are reported in one study each. The two inpatient studies both had some "other outcomes" that were associated with anorexia/appetite loss and some that were not. Thus, they are shown in both categories in the figure.

Finally, in a community-dwelling population from Germany receiving home care (*n* = 353), a significantly negative association (*P* < 0.001) was found between risk of malnutrition and physiological measures of nutritional body status (e.g., BMI, mid-upper arm circumference and calf circumference).[50]

One study specifically investigated an association between anorexia/appetite loss and malnutrition among older adults in Germany across different care settings: community (cohorts with and without home care) and institutional (geriatric day care and nursing home cohorts).[48] The association between appetite and malnutrition was significant in all cohorts regardless of residential setting in univariate analyses, and the odds of malnutrition were more than double in community-dwelling older adults without home care (OR [95% CI] = 2.42 [1.43, 4.10]), nearly four-fold greater for those receiving home care (OR [95% CI] = 3.99 [2.10, 7.58]) and eight-fold higher for geriatric day care subjects (OR [95% CI] = 8.01 [3.48, 18.44]),[48] reporting poor appetite after adjusting for covariates in a stepwise logistic regression analysis.
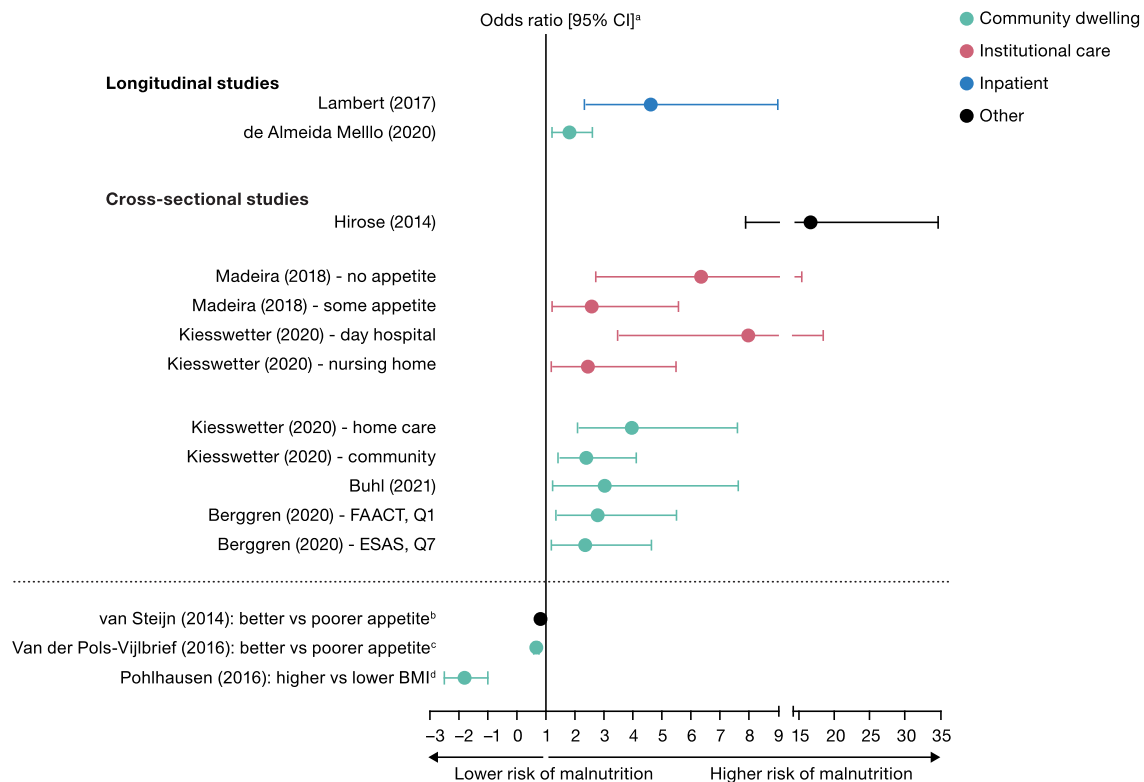
Figure 3 Relationship between anorexia/appetite loss and malnutrition in studies reporting odds ratios. Community-dwelling represents independent living or free living in the community. Institutional care represents living in a nursing care facility or care home. Inpatient represents being hospitalized or staying in a hospital ward. Other represents living in healthcare setting not covered (e.g., outpatient or conducted in mixed healthcare setting). Studies above the dashed line used better appetite as the reference group (positive odds ratio = more risk of malnutrition), whereas studies below the dashed line used worse appetite as the reference group (negative odds ratio = less risk of malnutrition). BMI, body mass index; CI, confidence interval; ESAS, Edmonton Symptom Assessment System; FAACT, Functional Assessment of Anorexia/Cachexia Treatment; Q, question. [a]Fifteen of the 58 studies identified investigated and reported a significant relationship between anorexia/poor appetite and malnutrition, with 10 studies presenting data as an odds ratio. [b]Odds ratio [95% CI] = 0.82 [0.70, 0.95]. [c]Unadjusted odds for better appetite associated with a lower risk of malnutrition, other studies were adjusted for baseline variables. [d]Univariate odds ratio for relationship between BMI and malnutrition (i.e., higher BMI is associated with a lower risk of malnutrition).

Relationship between anorexia/appetite loss and mortality

Eighteen of 35 (51.4%) longitudinal studies assessed the relationship between anorexia/appetite loss and mortality (*Table S5*). Mortality was assessed for up to 15 years of follow-up,[22] but studies most commonly reported associations with 1-year mortality (*n* = 6).[16,18,28,30,31] Anorexia/appetite loss was associated with increased risk of mortality in 17 of the 18 studies (94%; *Figure 4*), regardless of method used to assess anorexia/appetite loss (*Figure S1*). A positive association with mortality was noted across a variety of settings, including nine in community-dwelling older adults, six in an inpatient setting and two in an institutional setting (*Figure 4*). In 16 of the studies, the association between anorexia/appetite loss and mortality was maintained in multivariate analyses controlling for known confounders. Appetite loss increased the risk of death by 30–35% in the largest study

of > 1.4 million community-dwelling older people (hazard ratio [HR] [95% CI]: women = 1.30 [1.21, 1.39]; men = 1.35 [1.24, 1.48]).[16]

In a study of 296 older individuals admitted to hospital, a SNAQ Simplified score < 14 was associated with 2.62-fold increased odds of mortality at 6 months (OR [95% CI] = 2.62 [1.30, 5.27], *P* = 0.007).[25] In this study, every 1-point decrease in SNAQ Simplified score predicted a 22% increase in odds of 6-month mortality (OR [95% CI] = 1.22 [1.07, 1.39], *P* = 0.002) after adjustment for length of stay, Charlson comorbidity index and gender.[25] Similarly, another study reported that a SNAQ Simplified score < 14 was associated with more than two-fold higher risk of mortality (adjusted HR [95% CI] = 2.29 [1.12, 4.68], *P* = 0.023) in older women during acute hospitalization (*n* = 178).[26]

Anorexia/appetite loss was associated with a significantly higher risk of mortality in individuals with a range of comorbidities, including community-dwelling individuals with de-
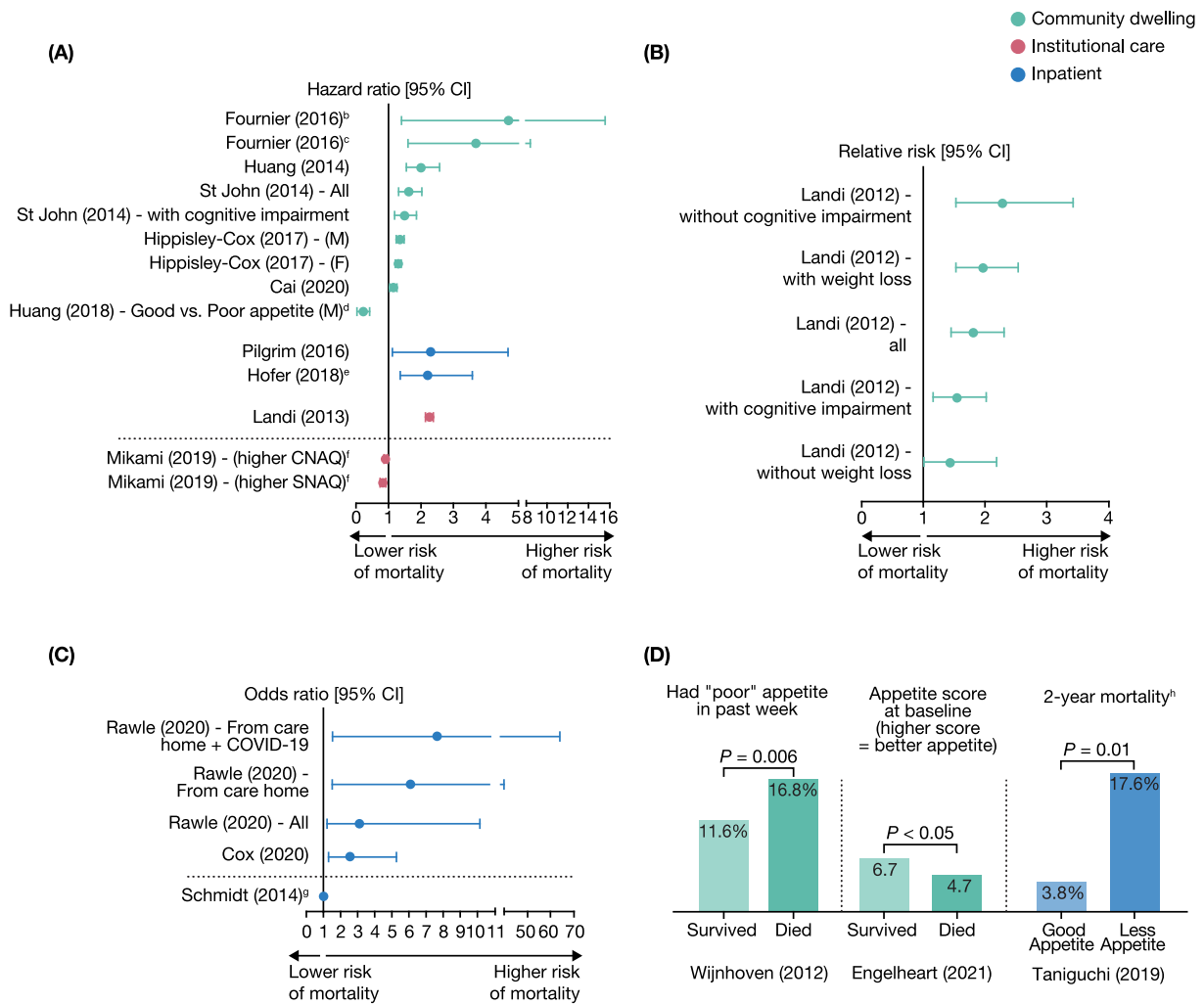
Figure 4 Relationship between anorexia/appetite loss and mortality[a]. (A) Data as hazard ratio. (B) Data as relative risk. (C) Data as odds ratio. (D) Other mortality data. CI, confidence interval; CNAQ, Council on Nutrition Appetite Questionnaire; COVID-19, coronavirus disease 2019; F, female; M, male; SNAQ, Simplified Nutritional Appetite Questionnaire. [a]Of the 58 studies identified, 18 longitudinal studies investigated the relationship between anorexia/poor appetite and mortality. Of these, 17 studies showed a significant association ($P < 0.05$) and are presented. [b]Five-year survival based on decline in appetite from baseline to 3 months. [c]Five-year survival based on decline in appetite from baseline to 6 months. [d]Analysis in female was non-significant. [e]Unadjusted hazard ratio, other studies adjusted for baseline variables as detailed in *Table S5*. [f]Data show that better appetite (i.e., higher CNAQ/SNAQ scores) is associated with lower risk of mortality. Findings agree with other studies showing that loss of appetite is associated with higher risk of mortality. [g]Odds ratio [95% CI] = 1.02 [1.00, 1.03], $P = 0.01$, with higher scores indicating better appetite (score inversely related to mortality). [h]One-year mortality was not significant for good appetite (3.8%) versus less appetite (5.9%), $P = 0.46$.

pressive disorder,[17] cognitive impairment[8,21] and weight loss[8] (*Table S5*). Three studies demonstrated that anorexia/appetite loss is associated with worse survival among subjects with cancer.[23,27,30]

The lone study that did not report a significant relationship between anorexia/appetite loss and mortality was a longitudinal Japanese study in haemodialysis outpatients that assessed the impact of quality of life on 3-year mortality.[32] Univariate Kaplan–Meier analysis demonstrated no significant difference in mortality for subjects aged $\geq$ 65 years with appetite scores > 75 (on 100 mm of visual analogue scale)

versus those with scores $\leq$ 74 ($P = 0.6832$).[32] In a multivariate analysis (adjusted for age, gender, duration of haemodialysis, clinical data and comorbidities), a small but statistically significant increased (rather than decreased) risk of mortality was observed in subjects aged $\geq$ 65 years with a better self-reported appetite (adjusted relative risk [95% CI] = 1.048 [1.006, 1.103], $P = 0.0247$).[32] The authors noted that the lack of correlation between appetite (and other measures) and mortality among subjects aged $\geq$ 65 years may be due to the low subject number ($n = 72$) because significant associations were seen in the larger cohort aged < 65 years.[32]

Relationship between anorexia/appetite loss and additional outcomes of interest

The relationship between anorexia/appetite loss and outcomes of interest other than malnutrition or mortality was examined in several studies, and results are summarized below, arranged by the number of studies (greatest to lowest number) for each outcome.

Sarcopenia indicators

Seven studies (four longitudinal and three cross-sectional) assessed the association of anorexia/appetite loss with sarcopenia indicators (*Figure 2* and *Table S6*).[26,35,36,42,56,64,65] A variety of methods were used to assess sarcopenia including risk of sarcopenia, sarcopenia incidence (3-year), grip strength, muscle strength, chair stand time, reduced muscle mass, absolute muscle mass, skeletal muscle mass, mobility and physical performance. In all three cross-sectional studies, the presence of anorexia/appetite loss was significantly associated with a higher risk of most, but not all, sarcopenia-related outcomes in older subjects.[56,64,65] The association between anorexia/appetite loss and the risk of sarcopenia was mixed in the four longitudinal studies.[26,35,36,42]

Decreased physical function

The association of anorexia/appetite loss with decreased physical function was evaluated in five longitudinal studies and one cross-sectional study (*Figure 2* and *Table S7*).[43–46,61,66] Assessments included subject-reported physical function, hospitalization-associated functional decline (Katz Index of Activities of Daily Living [ADL]), Functional Independence Measure ≥ 90, physical performance and functional change (Barthel Index or Instrumental ADL score). All but one[43] study reported a significant association between anorexia/appetite loss and decreased physical function.

Increased care

Six studies (five longitudinal and one cross-sectional) reported the association of anorexia/appetite loss and increased care requirements (*Figure 2* and *Table S8*).[26,38–40,43,61] Increased care was measured using a variety of definitions including receipt of formal or informal long-term care, entry/moved to nursing home or sheltered housing, discharged to higher level of care (includes death) and by residential accommodation type (habilitation/acute geriatric ward vs. nursing home vs. free living). Three of the studies noted an association between anorexia/appetite loss and the need for increased care.[38,40,61]

Hospitalization-related outcomes

The association between anorexia/appetite loss and hospitalization-related outcomes was assessed in four longitudinal studies (*Figure 2* and *Table S9*).[26,28,41,43] Outcomes included hospital utilization, time to first hospital or emergency room admission, hospital length of stay, readmission to hospital and hospitalization due to acute decompensated heart failure. Only one study found an association between anorexia/appetite loss and hospitalization-related outcomes.[28]

Falls

The association between anorexia/appetite loss and falls was assessed in three cross-sectional studies (*Figure 2* and *Table S10*).[55,60,62] Falls were measured as falls/fall-related injuries in the last 12 months or cognitive frailty-related falls. Anorexia/appetite loss was associated with a significantly increased risk of falls in two of the three studies.[55,60]

Health-related quality of life

Three studies (one longitudinal and two cross-sectional) reported the association between anorexia/appetite loss and health-related quality of life (HRQoL) (*Figure 2* and *Table S11*).[46,58,63] Methods to assess HRQoL included the Short Form-12 or -36 Health Surveys and global quality of life scores using the EORTC QLQ-C30. In two studies, good appetite was associated with better HRQoL.[46,63] In the remaining study, lack of appetite was associated with HRQoL, as assessed by the Short Form-12 mental, but not physical, component score.[58]

Cognition, depression and disability

Two studies (both cross-sectional) reported that anorexia/appetite loss was associated with poor cognition (*Figure 2* and *Table S12*).[60,61] Likewise, two cross-sectional studies reported that the likelihood of depression was higher in subjects with anorexia than in subjects without anorexia (*Figure 2* and *Table S12*).[61,66] Two longitudinal studies reported that anorexia/appetite loss was associated with a significantly higher risk of disability in unadjusted or non-fully adjusted models, but this association was not significant in fully adjusted models (*Figure 2* and *Table S12*).[7,37]

Other outcomes

The association between anorexia/appetite loss and other outcomes (e.g., hospital-acquired infection, treatment interruption, major adverse cardiac and cerebrovascular events [MACCE], life-threatening stroke, comorbidity burden, sleep quality and physical frailty) was assessed in six studies (three longitudinal and three cross-sectional) (*Figure 2* and *Table S13*).[26,28,47,57,59,61] Anorexia/appetite loss was significantly associated with hospital-acquired infection,[26] MACCE,[28] comorbidity burden,[61] frailty[57] and sleep efficiency.[59] In contrast, anorexia/appetite loss was not significantly associated with life-threatening stroke.[28] Anorexia/appetite loss was significantly associated with treatment interruption in a univariate, but not multivariate, analysis.[47]

Discussion

Although anorexia/appetite loss is common among older populations and represents a significant health-related burden, it is under-evaluated, under-diagnosed and under-treated in clinical practice.[73] Therefore, we sought to characterize the association of anorexia/appetite loss with negative outcomes using a comprehensive systematic search of published literature. Overall, 58 studies (both longitudinal and cross-sectional) in a variety of healthcare settings (community-dwelling, institutional care, inpatient and other) were identified that assessed the relationship of anorexia/appetite loss with mortality, morbidity and other healthcare outcomes in populations aged ≥ 65 years.

Key findings

A majority of studies (70.7%) reported on the prevalence of anorexia/appetite loss, although results varied greatly (from 0.20% to 63%).[16,43,67] This variation is explained, in part, by heterogeneity with respect to populations assessed, study design and the methods used to define and assess anorexia/appetite loss. A total of 15 studies examined the relationship between anorexia/appetite loss and malnutrition. As expected, each of these studies reported a statistically significant relationship between anorexia/appetite loss and malnutrition, including when adjusting for known confounders. Whereas the odds of malnutrition increased with anorexia/appetite loss regardless of healthcare setting, odds were increased in institutional-based studies versus community-based studies. One study, for example, demonstrated that the risk of malnutrition among those with anorexia/appetite loss was more than two-fold higher in a community setting and eight-fold higher in an institutional setting compared with those without anorexia/appetite loss.[48] A total of 18 studies examined the relationship between anorexia/appetite loss and mortality, with 17 (94.4%) showing a significant relationship, regardless of treatment setting. In 16 of the 17 studies, the association between anorexia/appetite loss and mortality remained significant after adjusting for known confounders. Whereas this association with mortality was expected among persons with cancer, it was also observed in other older populations with a range of comorbid conditions other than cancer. Other negative outcomes were studied less frequently in the literature, but associations between anorexia/poor appetite and sarcopenia, functional status, increased care, hospitalization, falls, HRQoL, cognition, depression, disability and other outcomes were also observed.

Associations of anorexia/appetite loss with these adverse outcomes are likely mediated via both direct and indirect mechanisms. Appetite loss will result in reduced food intake and precipitate or exacerbate weight loss, malnutrition, sarcopenia, declining strength and frailty, which in turn can impair functional status and HRQoL and increase falls, care requirements, hospitalizations, disability and mortality.[3] Specific micronutrient deficiencies may also mediate poor health outcomes associated with anorexia/appetite loss.[64] Relationships between anorexia/appetite loss may also be bi-directional. For example, whereas anorexia/appetite loss may contribute to the aetiology of multimorbidity, severe and chronic diseases may, in turn, drive anorexia/appetite loss.[18] Finally, associations of anorexia/appetite loss with adverse outcomes may not always represent a causal relationship. For example, diminished appetite may occur as a side effect of polypharmacy required for management of comorbidities, and these comorbidities may be the primary drivers of poor outcomes.[74]

The study of appetite loss and its health-related impact is complicated by a lack of standardized terminology describing the condition. In addition to appetite loss, terms such as poor appetite, reduced appetite, decreased appetite, lack of appetite, risk of malnutrition, undernutrition, malnourishment, weight loss, risk of weight loss, unexplained or abnormal weight loss, anorexia and anorexia of aging were used interchangeably across publications, geographies and settings. These terms, however, are not always equivalent. Clearer consensus definitions for, and more careful application of, these terms would be helpful for the field. For example, there is often a lack of distinction between anorexia (specific appetite loss) and malnutrition (lack of intake or uptake of nutrients).[75,76] Whereas malnutrition may be a secondary cause or symptom of anorexia, malnutrition can be caused by a variety of other physical or socioeconomic factors.[76]

The field is also complicated by the lack of a standardized and reliable method to define and assess anorexia/appetite loss. A wide range of methods were used in the 57 studies that described how anorexia/appetite loss was assessed (see *Tables 2* and *S3*). These included appetite-specific tools (e.g., SNAQ Simplified and CNAQ), nutritional assessment tools (e.g., SNAQ Short and MNA/MNA-SF), appetite-related questions from broader health-related tools (e.g., CES-D, EORTC QLQ-C30 and Edmonton Symptom Assessment System [ESAS]) and a variety of subject- or staff-reported assessments. As such, these tools vary in the breadth of what is actually assessed, ranging from a single appetite-specific question to a range of questions across various domains that include appetite. Even within more appetite-specific tools, such as the SNAQ Simplified, some questions extend beyond appetite to surrogates such as taste and meal frequency. Furthermore, these assessment tools vary greatly in terms of format (e.g., Likert, numeric rating scale or categorical), validation methodology, recall period (e.g., past day, past week, past month or not specified) and administration (e.g., subject-reported or staff-reported). This undoubtedly contributed to the great variation seen in prevalence estimates

and complicates comparisons across different studies. Although the SNAQ Simplified was the most frequently used tool, it was only utilized in approximately one quarter (*n* = 14) of the studies identified. Further, only 11 of these 14 studies used a consistent definition (SNAQ Simplified score of ≤ 14 or ≤ 13 out of 20) to define and report the prevalence of anorexia/appetite loss.

Gaps in the literature

There was also a notable paucity of information on the burden of anorexia/appetite loss in the United States (only 3 studies, 5.2%), with a majority of studies based in Europe (59%) or Asia (28%). This geographical discrepancy may reflect a heightened awareness of the role of nutrition in health and a holistic approach to patient management among geriatricians in Europe and Asia. Further, none of the US-based studies identified assessed the association of anorexia/appetite loss with mortality, malnutrition, sarcopenia, functional status, falls, cognition, depression or disability.

Whereas several studies examined the association of anorexia/appetite loss with malnutrition (*n* = 15) and mortality (*n* = 18), fewer studies examined the association with other outcomes (e.g., sarcopenia, functional status and HRQoL; see *Figure 2*), and no studies examined the association with healthcare costs, healthcare resource utilization (apart from basic information on hospitalization/length of stay or nursing home admission) and caregiver burden.

Strengths and limitations

The strength of this review is based on the systematic approach (following PRISMA guidelines) to study identification and the quality assessments performed on included studies (all studies except one[15] had low or medium risk of bias).

Despite the comprehensive, systematic approach, however, there are some limitations to our study. For example, it is not possible to rule out selection and publication bias as only English language studies were included. Additionally, although most studies utilized a multivariate analysis, it is difficult to separate out the effects of anorexia/loss of appetite from other comorbidities because not all studies adjusted for the same confounding variables. Likewise, there was substantial heterogeneity across studies in terms of country, population, appetite assessment, outcomes measured, hospital systems, medical technologies and healthcare settings, which may affect interpretation of our results. Despite these limitations, this comprehensive SLR provides robust evidence that anorexia/appetite loss increases the risk of a number of adverse outcomes, particularly mortality and malnutrition, in populations aged ≥ 65 years.

Conclusions

This SLR demonstrates that, among persons aged ≥ 65 years, anorexia/appetite loss is associated with increased risk of adverse outcomes (particularly malnutrition and mortality) across community living, nursing/care homes and inpatient settings and across disease states. These associations warrant efforts to improve the detection, evaluation and management of anorexia/appetite loss in older adults. Such efforts to improve management of anorexia/appetite loss are ongoing. The Society on Sarcopenia, Cachexia and Muscle Wasting Disorders, for example, will be publishing international guidelines on Anorexia of Aging shortly.[77] However, this SLR demonstrates that efforts are hindered by the lack of a standardized approach to appetite assessment and the lack of distinction between anorexia/appetite loss and malnutrition. Consensus guidance on the optimal appetite assessment tool in older populations, on the definition for anorexia/appetite loss in older adults and on standard of care would provide a much needed framework for intervention trials of candidate therapeutics for this target indication. In addition, there remains a need for well-designed longitudinal cohort studies (particularly in the United States) with clearly defined/standardized measures of anorexia/appetite loss and suitable control for confounding factors, including the interplay of factors such as malnutrition, cachexia, sarcopenia, cognitive decline, loss of mobility, social isolation and socioeconomic disadvantage.

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Conflict of interest

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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