REVIEW

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Association between skeletal muscle mass and quality of life in adults with cancer: a systematic review and meta-analysis

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Abstract

Low skeletal muscle mass is known to be associated with poor morbidity and mortality outcomes in cancer, but evidence of its impact on health-related quality of life (HRQOL) is less established. This systematic review and meta-analysis was performed to investigate the relationship between skeletal muscle mass and HRQOL in adults with cancer. Five databases (Ovid MEDLINE, Embase via Ovid, CINAHL plus, Scopus, and PsycInfo) were systematically searched from 1 January 2007 until 2 September 2020. Studies reporting on the association between measures of skeletal muscle (mass and/or radiodensity) derived from analysis of computed tomography imaging, and a validated measure of HRQOL in adults with cancer, were considered for inclusion. Studies classifying skeletal muscle mass as a categorical variable (low or normal) were combined in a meta-analysis to investigate cross-sectional association with HRQOL. Studies reporting skeletal muscle as a continuous variable were qualitatively synthesized. A total of 14 studies involving 2776 participants were eligible for inclusion. Skeletal muscle mass classified as low or normal was used to dichotomize participants in 10 studies ($n = 1375$). Five different cut points were used for classification across the 10 studies, with low muscle mass attributed to 58% of participants. Low muscle mass was associated with poorer global HRQOL scores [$n = 985$ from seven studies, standardized mean difference −0.27, 95% confidence interval (CI) −0.40 to −0.14, $P < 0.0001$], and poorer physical functioning domain HRQOL scores ($n = 507$ from five studies, standardized mean difference −0.40, 95% CI −0.74 to −0.05, $P = 0.02$), but not social, role, emotional, or cognitive functioning domain scores (all $P > 0.05$). Five studies examined the cross-sectional relationship between HRQOL and skeletal muscle mass as a continuous variable and found little evidence of an association unless non-linear analysis was used. Two studies investigated the relationship between longitudinal changes in both skeletal muscle and HRQOL, reporting that an association exists across several HRQOL domains. Low muscle mass may be associated with lower global and physical functioning HRQOL scores in adults with cancer. The interpretation of this relationship is limited by the varied classification of low muscle mass between studies. There is a need for prospective, longitudinal studies examining the interplay between skeletal muscle mass and HRQOL over time, and data should be made accessible to enable reanalysis according to different cut points. Further research is needed to elucidate the causal pathways between these outcomes.

Keywords Oncology; Body composition; Sarcopenia; Computed tomography; EORTC QLQ-C30; FACT

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Introduction

Suboptimal levels of some body composition parameters, particularly skeletal muscle, are predictive of poor cancer outcomes such as decreased overall survival,[1–5] shorter disease-free survival,[6–9] increased postoperative complications,[10–13] and increased chemotherapy toxicity.[14,15] Body composition analysis has therefore become an important method in oncology research. Cross-sectional areas (CSA) of skeletal muscle measured using analysis of computed tomography (CT) imaging are highly correlated with whole body stores,[16] and the mean radiodensity of this CSA is considered a marker of fatty infiltration,[17] providing a convenient source of body composition data in patients who routinely undergo radiological imaging for cancer diagnosis, staging, and monitoring.[18]

Traditional morbidity and mortality endpoints are now being complemented by other outcome measures as enhancements in life-prolonging treatments bring about improved survival rates in people with cancer.[19–21] Consequently, measurement of health-related quality of life (HRQOL) has become increasingly important in evaluating effectiveness of health interventions.[22,23] HRQOL is a subjective and complex outcome and is understood to encompass core domains of physical, psychological, social, and functional wellbeing.[19,24] Cancer diagnosis and treatment can affect HRQOL across the spectrum of these interacting domains,[25] and the use of validated, cancer-specific HRQOL assessment tools allows for an insight into the relationship between a patient's overall wellbeing, life satisfaction, and health status in the context of their disease.[20,24,26] Understanding HRQOL is key to patient-centred care, enabling researchers and clinicians to identify a need for supportive interventions, informing treatment decision making, and challenging assumptions about what patients consider important.[24]

There is some evidence that low skeletal muscle mass measured using CT imaging analysis is linked to reduced HRQOL in patients with cancer.[27,28] It is hypothesized that this relationship between skeletal muscle mass and HRQOL reflects the interplay between reduced strength and impaired physical function, with independence and emotional wellbeing.[27–29] In a 2017 cross-sectional study of 734 newly diagnosed non-small cell lung cancer patients, low muscle mass was demonstrated to negatively affect physical and role functioning domains of HRQOL in both genders, and overall HRQOL in male patients.[27] Similarly, a 2018 cross-sectional study of 237 patients with incurable lung and gastrointestinal cancers found that low skeletal muscle was associated with worse overall HRQOL and greater symptoms of depression.[28] The evidence-base is still emerging, and this association requires further exploration so that effective interventions that improve HRQOL are developed. This systematic review and meta-analysis was performed to investigate the relationship between CT-derived measures of skeletal muscle mass, and HRQOL in adults with cancer.

The specific aims of this review were to (i) compare HRQOL scores between adults with either low or normal skeletal muscle mass and (ii) to examine the correlation between skeletal muscle mass and HRQOL. The secondary aims were to examine the relationship between change in skeletal muscle mass and change in HRQOL and to examine the correlation between CT-derived skeletal muscle radiodensity and measures of HRQOL.

Methods

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis guidelines.[30] This review was prospectively registered with the PROSPERO international database of systematic reviews on 26 December 2020, prior to data extraction and analysis (CRD42020198972). In a deviation to the published protocol, measures of adipose tissue were excluded as a secondary outcome due to the small number of included studies reporting on its association to HRQOL.

Data sources and search strategy

A systematic search of the Ovid MEDLINE, Embase via Ovid, CINAHL plus, Scopus, and PsycInfo databases was conducted on 2 September 2020. A combination of keywords and subject headings such as 'sarcopenia', 'skeletal muscle', 'quality of life', and 'cancer' were used for each database; details of search terms for each database are available in Supporting Information, *Appendix* S1. The search was run from 1 January 2007 until present, with dates chosen to ensure all relevant studies since the first published use of this technique in the oncology population[31] were captured.

Study selection criteria

Full text studies reporting on the relationship between body composition assessed using CT imaging analysis (Intervention), with HRQOL assessed using a validated tool (Outcome), in adults aged over 18 years with any cancer at any stage of treatment (Population), were eligible for inclusion. Analysis of the association between CT-derived skeletal muscle index (SMI, cm^2/m^2) or cross-sectional skeletal muscle area (cm^2), and global HRQOL scores at baseline was considered the primary outcome; the term 'global' is hereafter used to refer to 'global', 'overall', or 'total' HRQOL scores, depending on the tool used for assessment. Domain HRQOL scores, longitudinal changes in skeletal muscle mass and/or HRQOL, and skeletal muscle radiodensity measured as mean Hounsfield Units (HU)

of the cross-sectional skeletal muscle area and analysed in relation to HRQOL, were secondary outcomes. Studies not published in the English language, conference abstracts, narrative review articles, and letters to the editor were excluded. Reference lists of all studies meeting inclusion criteria were hand searched. Individual studies included within systematic reviews were also screened for relevance. For studies meeting the above inclusion criteria but not reporting an analysis of the association between body composition and HRQOL, study authors were contacted for further information.

Following database searching, references were exported to Endnote X9[32] for removal of duplicates. Article titles and abstracts were independently screened by two researchers using Covidence systematic review software.[33] Full text articles were then independently reviewed by the same individuals for inclusion against the eligibility criteria. At each stage, consensus was achieved through discussion prior to progression of screening.

Data extraction

A template was created to facilitate extraction of data from included studies, for synthesis and potential meta-analysis. One researcher extracted data relating to study characteristics: author, year of publication, study design, country of origin, setting, patient demographics (number of participants, cancer type and stage, age, and gender), body composition assessment data (software used, tissue types measured and radiodensity ranges used, anatomical site of analysis, timing/frequency of body composition measurements, and thresholds for determination of optimal vs. suboptimal values), and HRQOL assessment data (validated tool used, timing/frequency of assessment, and HRQOL scores). Two researchers independently extracted primary outcome data related to low muscle mass prevalence and associations between skeletal muscle mass and global scores of HRQOL at baseline. Discrepancies in data extraction were addressed by repeat review of relevant studies, to ensure accuracy. One researcher extracted secondary outcome data relating to associations between skeletal muscle mass and domain HRQOL scores, changes in skeletal muscle and HRQOL over time, and association between skeletal muscle radiodensity and baseline HRQOL scores.

Results synthesis and statistical analysis

Studies classifying skeletal muscle mass as a dichotomous variable (low or normal) using published SMI cut points, or based on a priori classification of clinically relevant muscle mass loss, were combined in a meta-analysis to investigate cross-sectional association with HRQOL. Study authors were contacted to request recalculation of data using a published SMI cut point appropriate for their cohort, if this was not reported in their original publication. Meta-analysis was performed using RevMan software (Version 5.4),[34] using inverse variance analysis with a random effects model due to study heterogeneity. Standardized mean differences with 95% confidence intervals (CI) were calculated as the summary effect measure, as all of the HRQOL tools used in the studies included in the meta-analysis were scored in the same direction (lower scores reflecting worse HRQOL).[35] A standardized mean difference of 0.2, 0.5, and 0.8 was interpreted to represent small, moderate, and large effect, respectively.[36] Where possible, HRQOL data were in the form of mean ± standard deviation for each category of muscle mass (low or normal). For studies reporting 95% CI, data were converted to standard deviation according to published guidelines.[35] Subgroup separation of studies was used in forest plot presentations to distinguish studies presenting data as mean difference between low and normal muscle mass. This subgroup analysis additionally functioned as a sensitivity analysis, enabling examination of the impact of including studies reporting multivariate data where adjustments were made for important confounding variables, compared with studies reporting univariate data only. Meta-analyses for global HRQOL and the physical function domain were repeated, with studies alternatively grouped based on the cut point used to stratify participants with low or normal muscle mass, to examine if there is differentiation of pooled data from studies using different cut points. Statistical heterogeneity was assessed using interpretation of the I^2 value, where I^2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively.[37]

Primary and secondary outcome data not suitable for meta-analysis due to use of incompatible statistical tests or HRQOL domain scores were synthesized qualitatively.

Quality assessment

Each of the included studies was assessed for quality and risk of bias by two reviewers, using the Academy of Nutrition and Dietetics Quality Checklist for Primary Research.[38] Assessments were undertaken independently, and then, a consensus was formed through group discussion with a third reviewer to resolve conflicts. Comparability of study groups was marked as 'N/A' when groups were defined by outcome rather than randomization, or if there was only one group (Question 3). For studies in which CT-derived body composition was a primary outcome, detailed description of methodology required listing the site of analysis, software used, and radiodensity reference ranges for identification of tissue types, as a minimum standard for quality in reporting (Question 6). For studies in which the primary research question differed to that of this review, statistical analysis was deemed

to be appropriate if statistical tests used were able to address the study's aims (Question 8).

Results

Study selection

The systematic literature search yielded 6090 studies after removal of duplicates (*Figure* 1). Following title and abstract screening, 5892 studies were excluded. Full text review of 198 studies was conducted; reasons for exclusion are shown in *Figure* 1. Authors from 13 studies were contacted via email seeking further data if the paper reported measures of CT-derived body composition along with HRQOL scores but did not report an analysis of the relationship between these variables. A total of 14 studies met the criteria for inclusion.[27,28,39–50]

Study characteristics

Table 1 summarizes the characteristics of the 14 included studies. Analysis of associations between CT-derived body composition and HRQOL was conducted for 2776 participants

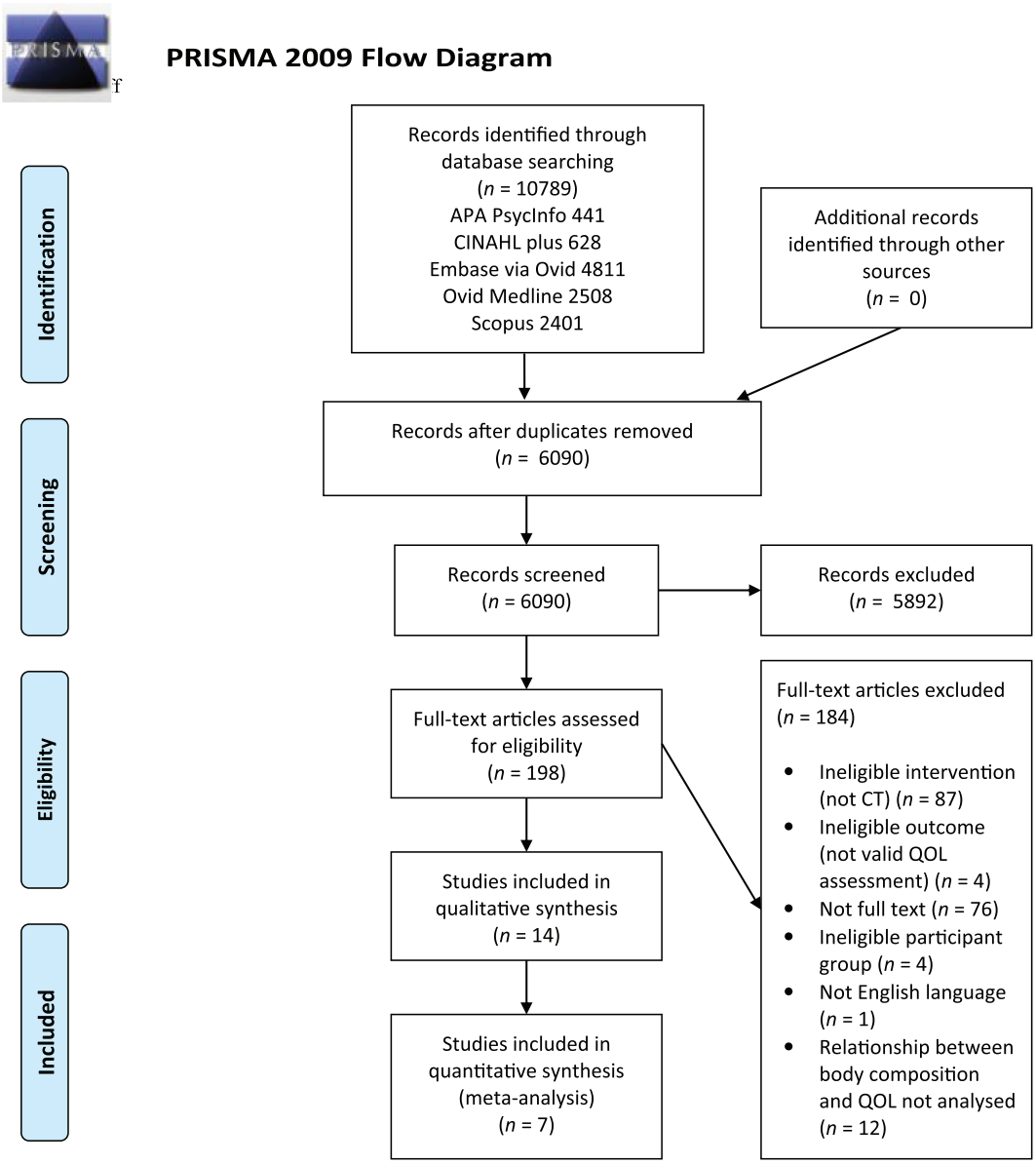

Figure 1 Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow diagram of study selection.

Table 1 Characteristics of included studies listed by HRQOL assessment tool

Author (year)	Country	Study design	Cancer type/s	Sample size	Gender, Female *n* (%)	Setting	Age, years, mean ± SD	Body composition analysis software	Body composition measure (s)	Site of CT analysis	HRQOL assessment tool
Gigic *et al.* (2020)[43]	Germany	Prospective cohort	Colorectal	138	39 (28)	Outpatient	61 ± 11.5	Syngo Volume tool	SMI VFA SFA	L3/4	EORTC QLQ-C30
Derksen *et al.* (2020)[42]	Netherlands	Prospective cohort	Colorectal	221	79 (36)	Outpatient	63.5 ± 8.4	SliceOmatic	SMI	L3	EORTC QLQ-C30
Daly *et al.* (2020)[41]	Ireland, Scotland	Cross-sectional	Gastrointestinal (40%) Lung (26%) Other (34%)[a]	1027	503 (49)	Inpatient and outpatient	Median (IQR) 66 (57–74)	Ireland: OsiriX software version 4.1.1 Scotland: ImageJ software (version 1.47)	SMI MA	L3	EORTC QLQ-C30
Blauwhoff-Buskermolen *et al.* (2017)[40]	Netherlands	Cross-sectional	Colorectal Lung Breast Prostate	241	111 (46)	Outpatient	64 ± 10	SliceOmatic	SMI	L3 or T4	EORTC QLQ-C30
Bye *et al.* (2017)[27]	Norway	Cross-sectional	Lung	734	314 (43)	Outpatient	65.4 ± 9.4	SliceOmatic	SMI SMD	L3	EORTC QLQ-C30 EORTC QLQ-LC13
Huang *et al.* (2017)[45]	China	Before–after	Gastric	110	29 (26)	Outpatient	63.2 ± 10.4	INFINITT Healthcare Version 3.0.11.3	SMI	L3	EORTC QLQ-C30 EORTC QLQ-STO22
van Roekel *et al.* (2017)[49]	Netherlands	Cross-sectional	Colorectal	104	42 (40)	Outpatient	64.3 ± 9	SliceOmatic	SMI VAT IMAT MA	L3	EORTC QLQ-C30
Thoresen *et al.* (2012)[48]	Norway	Prospective cohort	Colorectal	50	24 (48)	Outpatient	Median (IQR) 64 (41–85)	SliceOmatic	SMI	L3	EORTC QLQ-C30
Aleixo *et al.* (2020)[39]	USA	Cross-sectional	Breast	99	99 (100)	Outpatient	56.4 ± 13.1	SliceOmatic	SMI SMD SMG	L3	FACT-G
Sheean *et al.* (2019)[47]	USA	Cross-sectional	Breast	41	41 (100)	Outpatient	59.6 ± 11.9	SliceOmatic	SMI SMD VAT SAT TAT	L3	FACT-B FACT-ES
Nipp *et al.* (2018)[28]	USA	Cross-sectional	Lung (56.5%) Gastrointestinal (43.5%)	237	109 (46)	Outpatient	64.4 ± 10.9	OsiriX	SMI	L3	FACT-G
Hua *et al.* (2020)[44]	China	Before–after	Nasopharyngeal	56	9 (16)	Outpatient	44.2 ± 10.93	Monarco TPS	SMI	C3 (converted to L3)[b]	WHOQOL-100

(*Continues*)

Table 1 (continued)

Author (year)	Country	Study design	Cancer type/s	Sample size	Gender, Female *n* (%)	Setting	Age, years, mean ± SD	Body composition analysis software	Body composition measure (s)	Site of CT analysis	HRQOL
assessment tool											
Mitsui *et al.* (2020)[46]	Japan	Retrospective cohort	Prostate	301	301 male (100)	Outpatient	Median (IQR) 68 (63–71)	Synapse Vincent V4	SMI VATI SATI	L3	EPIC
Wang *et al.* (2016)[50]	USA	Before–after	Oropharyngeal	50	2 (4)	Outpatient	57 ± 7	MATLAB version 13.0	Total psoas area Lean psoas area SMD	L4	UWQOL HNQOL

[a]Breast, gynaecologic, genitourinary, neurologic, haematological, melanoma, unknown primary, and others.
[b]Skeletal muscle area at L3 estimated using published formula.[51]
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30[20]; EORTC QLQ-STO22, Gastric cancer module[52]; EPIC, Expanded Prostate Cancer Index Composite instrument[53]; FACT-G, Functional Assessment of Cancer Therapy – General[54]; FACT-B, Breast[55]; FACT-ES, Endocrine Symptoms[56]; HNQOL, Head and Neck Quality of Life Instrument[57]; HRQOL, health-related quality of life; HU, Hounsfield Units; IMAT, intermuscular adipose tissue; IQR, interquartile range; MA, mean muscle attenuation [mean radiodensity (in HU) of cross-sectional muscle area]; PD1, first progression of disease; SAT, subcutaneous adipose tissue (interchangeable with SFA); SATI, subcutaneous adipose tissue index; SD, standard deviation; SFA, subcutaneous fat area (interchangeable with SAT); SMD, skeletal muscle radiodensity (a measurement of MA); SMG, skeletal muscle gauge (SMI × SMD); SMI, skeletal muscle index; SMM, skeletal muscle mass; TAT, total adipose tissue (SAT + VAT); TPA, total psoas area; UWQOL, University of Washington Quality of Life Instrument[58]; VAT, visceral adipose tissue (interchangeable with VFA); VATI, visceral adipose tissue index; VFA, visceral fat area (interchangeable with VAT); WHOQOL-100, The World Health Organization Quality of Life assessment.[59]

in total. Colorectal cancer was the most frequently reported cancer type,[40,42,43,48,49] followed by lung,[27,28,40,41] breast,[39,40,47] gastrointestinal,[28,41,45] prostate,[40,46] head and neck,[44,50] and 'other' cancers such as gynaecologic, genitourinary, neurologic, haematological, melanoma, and unknown primary.[41] Cancer stage of participants included early/operable disease[39,45,46,49] and advanced disease[27,28,40–42,47,48]; three studies involved both staging groups.[43,44,50] Treatment status at the time of CT imaging used for analysis of body composition was not always clearly described. In one study, CT imaging was conducted prior to any surgery or chemoradiation.[50] In the study by Gigic *et al.*,[43] CT imaging used for analysis was conducted prior to surgery for the whole cohort, but 38% of participants had already commenced chemotherapy, and in the study by Blauwhoff-Buskermolen *et al.*,[40] all participants were chemotherapy naïve, but 15% of participants had required surgery in the previous 6 months. In all other included studies, participant history of chemotherapy, radiotherapy, and/or surgery at the point of CT imaging was unclear.

Body composition analyses

Body composition analysis was conducted on CT images of the lumbar spine in all but one study,[44] most frequently at the level of the third lumbar vertebra (L3) (*Table* 1). Most studies used the same radiodensity range of −29 to +150 HU for identification of skeletal muscle during CT imaging analysis; Gigic *et al.*[43] used a more narrow range of 40 to 100 HU based on plausibility testing of their cohort in a previous publication,[60] and Aleixo *et al.*[39] did not report the specific radiodensity range used. Wang *et al.*[50] alternatively used tracing of psoas muscle borders to determine cross-sectional skeletal muscle area.

Analysis of skeletal muscle

Ten studies categorized a total of 1375 participants according to baseline skeletal muscle mass using a range of cut points, presented in *Table* 2. In nine studies,[28,40–42,44,46–49] widely used cut points based on association with mortality in cancer patients,[1,3] or consensus guidelines for diagnosis of cancer cachexia,[61] were used to dichotomize participants as having either low muscle mass or not. The study by Huang *et al.*[45] used a percentage change in SMI pre-surgery to post-surgery (≥10% vs. <10%) to dichotomize low and normal muscle mass, as this extent of muscle loss was deemed clinically relevant.[62] Across the 10 studies, 795 participants (58%) were classified as having low muscle mass.

Six studies assessed the relationship between skeletal muscle mass and quality of life using continuous linear associations of correlation or linear regression.[27,39,41–43,50] There

Table 2 Studies with participants grouped according to baseline skeletal muscle mass (low or normal)

Author (year)	Sample size[a] (% of whole study)	Cancer type/s Stage	Treatment status at point of baseline CT image	Cut point for low muscle mass		Source of cut point	Low muscle mass prevalence, *n* (%)	Timing of HRQOL assessments	Analysis type
				Women	Men				
Daly *et al*. (2020)[41]	428 (41.7)	Gastrointestinal Lung Other Stages III–IV Incurable	81% receiving active palliative chemotherapy Unclear treatment and surgical status	<41 cm^2/m^2	<43 cm^2/m^2 if BMI < 25 kg/m^2 <53 cm^2/m^2 if BMI ≥ 25 kg/m^2	Martin *et al*. 2013[1]	192 (45)	Baseline only (within 12 weeks of CT)	Multivariate Adjusted for weight loss, ECOG-PS, mGPS, and low MA
Derksen *et al*. (2020)[42]	221 (100)	Colorectal Stage IV Unresectable	Post-chemotherapy treatment Prior surgical resection in unspecified number of participants	<41 cm^2/m^2	<43 cm^2/m^2 if BMI < 25 kg/m^2 <53 cm^2/m^2 if BMI ≥ 25 kg/m^2	Martin *et al*. 2013[1b]	117 (53)	Baseline (enrolment) Every 9 weeks until PD1	Univariate
Mitsui *et al*. (2020)[46c]	301 (100)	Prostate Stages I–III Resectable	Chemo/radiotherapy status not reported Pre-surgery	—	<43 cm^2/m^2 if BMI < 25 kg/m^2 <53 cm^2/m^2 if BMI ≥ 25 kg/m^2	Martin *et al*. 2013[1]	91 (30)	Baseline (pre-surgery) 2 weeks, 1 month, 3 months, 6 months, 12 months post-surgery	Multivariate Adjusted for significant variables on univariate analysis: HT and VAT/SAT ≥ 1.35
Hua *et al*. (2020)[44]	56 (100)	Nasopharyngeal Stages II–IV	Pre-CCRT Unclear surgical status	<41 cm^2/m^2	<43 cm^2/m^2 if BMI < 25 kg/m^2 <53 cm^2/m^2 if BMI ≥ 25 kg/m^2	Martin *et al*. 2013[1]	34 (61)	Baseline (mid-point of CCRT, at 15F) 3 weeks post baseline	Univariate
Sheean *et al*. (2019)[47d]	41 (100)	Breast Stage IV	Mixed/unclear treatment status Prior surgery in 30 participants (73%)	<41 cm^2/m^2	—	Martin *et al*. 2013[1]	14 (34)	Baseline only (during treatment)	Univariate
Nipp *et al*. (2018)[28]	237 (100)	Lung (56.5%) Gastrointestinal (43.5%) Unresectable	Mixed/unclear treatment status	<39 cm^2/m^2	<55 cm^2/m^2	Fearon *et al*. 2011[61]	131 (55)	Baseline (within 30 days before/after CT)	Multivariate Adjusted for gender, age, marital status, education, and cancer type
Blauwhoff-Buskermolen *et al*. (2017)[40e]	241 (100)	Colorectal III–IV Lung, Breast, Prostate Stage IV	Pre-palliative chemotherapy Prior surgery in past 6 months in 37 participants (15%)	Colorectal, breast, prostate cancer <39 cm^2/m^2 Lung cancer <51.9 cm^2/m^2	<55 cm^2/m^2 <66.0 cm^2/m^2	Fearon *et al*. 2011[61] Unpublished cut point for CT imaging at T4[f]	142 (59)	Baseline (pre-palliative chemotherapy)	Univariate
	110 (100)	Gastric					35 (32)		Univariate

(*Continues*)

Table 2 (continued)

Author (year)	Sample size[a] (% of whole study)	Cancer type/s Stage	Treatment status at point of baseline CT image	Cut point for low muscle mass		Source of cut point	Low muscle mass prevalence, *n* (%)	Timing of HRQOL assessments	Analysis type
				Women	Men				
Huang *et al*. (2017)[45]		Stages I–III	Chemo/ radiotherapy status not reported Pre-surgery (<1 month)	Muscle mass loss ≤10% from baseline to 1 week post-surgery		Puthucheary *et al*. 2013[53]		1, 3, and 6 months post-surgery	
van Roekel *et al*. (2017)[49]	92 (88)	Colorectal Stages I–III (5.2 ± 1.7 years)	Pre-chemo/ radiotherapy treatment in 93% of participants, post-commencement of treatment (4–36 days) in 7% of participants Surgical status not reported Multivariate Adjusted for gender, age at diagnosis, BMI at HRQOL assessment, number of comorbidities, tumour stage, and chemotherapy treatment	<41 cm^2/m^2	<43 cm^2/m^2 if BMI < 25 kg/m^2 <53 cm^2/m^2 if BMI ≥ 25 kg/m^2	Martin *et al*. 2013[1]	29 (32)	Once only, 2–10 years post-diagnosis	
Thoresen *et al*. (2012)[48]	28 (56)	Colorectal Stage IV	Mixed/unclear chemo/ radiotherapy treatment and surgical status for subgroup of participants in current analysis	≤38.5 cm^2/m^2	≤52.5 cm^2/m^2	Prado *et al*. 2008[3]	10 (36)	Once only (within 30 days of CT)	Univariate Multivariate Adjusted for age and gender

[a]Sample size: number of participants included in analysis of relationship between skeletal muscle mass and HRQOL.
[b]In the original publication, skeletal muscle index was categorized as loss (>2% loss), stable (≤2% loss to ≤2% gain), or gain (>2% gain). Upon our request, the authors repeated the analysis using their choice of preferred cut point for categorization of participants into two groups.
[c]Not included in meta-analysis due to use of a prostate cancer-specific tool, which does not generate a global score.
[d]Not included in meta-analysis due to incompatible data [presented as median (interquartile range)].
[e]Groups defined using diagnosis of cachexia, using cut point in addition to weight loss >2% in previous 6 months.
[f]According to study authors, values based on Fearon *et al*.[61] cut off for lumbar (L3) CT imaging analysis, in an unpublished study of patients with SMI data for both L3 and T4.
CCRT, concurrent chemoradiotherapy; ECOG-PS, Eastern Cooperative Oncology Group Performance Status[63]; HT, hypertension; MA, mean muscle attenuation; mGPS, modified Glasgow Prognostic Score (a measure of systemic inflammation)[64]; SAT, subcutaneous adipose tissue; PD1, first progression of disease; VAT, visceral adipose tissue.

was heterogeneity in the assessment of the relationship and data reported; thus, these results were synthesized qualitatively.

Two studies investigated the association between HRQOL and SMI as both a categorical and continuous variable.[41,42]

HRQOL assessment tools

The most frequently utilized HRQOL assessment tool was the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30),[20] used in eight studies.[27,40–43,45,48,49] The Functional Assessment of Cancer Therapy (FACT) scale[54] was used in three studies: one study used the 27 item general scale (FACT-G),[28] and two studies[39,47] used the breast cancer-specific version of this tool (FACT-B).[55] Other tools used for quality of life assessment are reported in *Table* 1.[52,56–59,65] Global or overall HRQOL was measured in 12 studies (n = 2425); in a majority of studies (nine studies, n = 2048, 84%),[27,40–45,48,49] this measure was derived through dedicated items in the questionnaire using the EORTC QLQ-C30 or WHOQOL-100.[20,59] In three studies (n = 377, 16%),[28,39,47] overall HRQOL was determined as a sum of individual domain scores using the FACT scale.[54]

Timing of baseline HRQOL assessments

Baseline HRQOL assessment was conducted within 1 month of CT imaging in four studies,[27,28,45,48] and within 3 months in two studies.[41,47] In seven studies,[39,40,42–44,46,50] timing of HRQOL in relation to CT imaging was not specified. Rather, the two assessments were reported as occurring at around the same period of time in the context of participants' treatment; prior to surgery,[43,46] chemo and/or radiotherapy,[39,40,44,50] or enrolment in a research trial.[42] One study[49] conducted HRQOL assessments between 2 and 10 years following body composition analysis and was included in meta-analysis as it was the first and only time point of HRQOL assessment.

Follow-up assessments

Two studies used repeat CT imaging analysis to assess longitudinal changes in body composition for analysis against changes in HRQOL.[42,50] Meta-analysis of follow-up HRQOL data was not possible, due to the heterogeneity in timing and assessment measures used.

Quality assessment of included studies

A summary of the quality criteria checklist assessing the relevance and validity of included studies is presented in *Table* 3. In all studies, the process of participant selection was subject to bias, as only patients for whom a routinely conducted CT image was available for baseline assessment were eligible for inclusion. Bias in participant selection was also demonstrated in other criteria such as inclusion of participants with a particular language background or treatment plan. Because of this bias, all studies included in this review were assigned a 'no' for the second validity criteria question at a minimum, and therefore received a 'neutral' quality rating. All studies received a rating of N/A for the question of study group comparability, as participants were either not grouped, or they were grouped according to body composition variable outcomes. One study provided only a brief description of CT-derived body composition methodology,[39] all other studies reported sufficient detail of this methodology relevant to their primary outcomes. In four studies, investigators conducting body composition analysis were blinded to participant details[27,41,42,47]; in the remaining 10 studies, it was unclear whether blinding occurred.

Primary outcome: Association of muscle mass with global HRQOL scores at baseline

Seven of the studies outlined in *Table* 2 used HRQOL assessment tools that produced a global health score.[28,40,42,44,45,48,49] Meta-analysis of pooled HRQOL global score data from a total of 985 participants is presented in *Figure* 2. The first forest plot subgroup contains five studies in which data were univariate, without adjustment for confounding factors.[40,42,44,45,48] Data from two studies were multivariate (second subgroup).[28,49] The summary effect measure from all seven studies showed that skeletal muscle mass below an optimum threshold was associated with poorer global HRQOL scores (standardized mean difference −0.27, 95% CI −0.40, −0.14, small effect size). Inclusion of both univariate and multivariate data did not affect the significance of the pooled result. There was very low statistical heterogeneity within these data (I^2 = 2%). The inclusion or exclusion of van Roekel *et al*.[49] (where follow-up HRQOL was 2–10 years post-CT analysis) did not affect the findings of the meta-analysis (data not shown). As five different cut points were applied across the seven studies to classify participants with low or normal muscle mass, the meta-analysis was repeated with studies grouped according to cut point used (*Figure* 2A, presented in *Appendix S2*). Statistical analysis of the subgroups was not possible due to the small number of studies[35]; however, the visual assessment of the forest plots did not indicate there was evidence of systematic bias (*Figure* 2A).

The study by Sheean *et al*.[47] assessed the relationship between skeletal muscle as a categorical variable and global HRQOL scores but was not included in the meta-analysis as

Table 3 Quality assessment of included studies

Academy of Nutrition and Dietetics Quality Criteria Checklist for Primary Research	Aleixo *et al.* (2020)[39]	Blauwhoff-Buskermolen *et al.* (2017)[40]	Bye *et al.* (2017)[27]	Daly *et al.* (2020)[41]	Derksen *et al.* (2020)[42]	Gigic *et al.* (2020)[43]	Hua *et al.* (2020)[44]
Overall quality rating	Ø	Ø	Ø	Ø	Ø	Ø	Ø
Relevance questions							
Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the intervention or procedure feasible?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Validity questions							
1. Was the research question clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the selection of study subjects/patients free from bias?	No	No	No	No	No	No	No
3. Were study groups comparable?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4. Was method of handling withdrawals described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was blinding used to prevent introduction of bias?	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
6. Were intervention/therapeutic regimes, exposure factor or procedure and any comparisons(s) described in detail? Were intervening factors described?	No[a]	Yes	Yes	Yes	Yes	Yes	Yes
7. Were outcomes clearly defined and the measurements valid and reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Are conclusions supported by results with biases and limitations taken into consideration?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Is bias due to study's finding or sponsorship unlikely?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

The Academy of Nutrition and Dietetics Quality Checklist for Primary Research contains four relevance questions, and 10 validity questions assessing the means by which the study has addressed issues of bias and generalisability, and quality in reporting of methods and statistical analysis.[37] Studies are assigned a positive (+) rating if these factors are adequately addressed with a 'yes' assigned to most questions, a negative (−) rating if they are not, and a neutral (Ø) rating if the answers to particular validity questions (2, 3, 6, and 7) are 'no', indicating a lack of strength in quality.

[a]Specific radiodensity range used to identify skeletal muscle through CT imaging analysis not reported in methods.

data were presented as median (interquartile range). This small study (n = 14 low muscle mass, n = 27 normal muscle mass) found no difference in global HRQOL scores between the two groups using both the FACT-B tool [low muscle mass 108 (93–119) vs. normal muscle mass 100 (87–118) P = 0.29] and the FACT-ES tool [low muscle mass 174 (151–191) vs. normal muscle mass 158 (142–178) P = 0.10]; for both tools, a higher score represents a higher HRQOL. Subgroup analysis suggested that obesity may be a confounding variable in the analysis, with those who were obese reporting poorer HRQOL.[47]

Five studies reported on the relationship between skeletal muscle stores as a continuous variable and global HRQOL scores at baseline, presented in *Table* 4.[27,39,41–43] Four studies found weak associations, which were not statistically significant.[39,41–43] In large study of advanced lung cancer patients (n = 734), Bye *et al.*[27] reported a significant association between SMI and global HRQOL in male patients in both univariate analysis (P = 0.001) and after adjusting for age and tumour stage ($P < 0.05$); in this non-linear analysis, global HRQOL scores deteriorated once SMI fell to a breakpoint of 42–45 cm^2/m^2.

Table 3 (continued)

Academy of Nutrition and Dietetics Quality Criteria Checklist for Primary Research	Huang *et al.* (2017)[45]	Mitsui *et al.* (2020)[46]	Nipp *et al.* (2018)[28]	Sheean *et al.* (2019)[47]	Thoresen *et al.* (2012)[48]	van Roekel *et al.* (2017)[49]	Wang *et al.* (2016)[50]
Overall quality rating	Ø	Ø	Ø	Ø	Ø	Ø	Ø
Relevance questions							
Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the intervention or procedure feasible?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Validity questions							
1. Was the research question clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the selection of study subjects/patients free from bias?	No	No	No	No	No	No	No
3. Were study groups comparable?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4. Was method of handling withdrawals described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was blinding used to prevent introduction of bias?	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
6. Were intervention/therapeutic regimes, exposure factor or procedure and any comparisons(s) described in detail? Were intervening factors described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Were outcomes clearly defined and the measurements valid and reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Are conclusions supported by results with biases and limitations taken into consideration?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Is bias due to study's finding or sponsorship unlikely?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

The Academy of Nutrition and Dietetics Quality Checklist for Primary Research contains four relevance questions, and 10 validity questions assessing the means by which the study has addressed issues of bias and generalisability, and quality in reporting of methods and statistical analysis.[37] Studies are assigned a positive (+) rating if these factors are adequately addressed with a 'yes' assigned to most questions, a negative (−) rating if they are not, and a neutral (Ø) rating if the answers to particular validity questions (2, 3, 6, and 7) are 'no', indicating a lack of strength in quality.

[a]Specific radiodensity range used to identify skeletal muscle through CT imaging analysis not reported in methods.

Secondary outcomes

Association of skeletal muscle mass with domain HRQOL scores at baseline

Meta-analysis of physical function domain HRQOL scores at baseline included 507 participants across five studies[42,44,45,48,49] (*Figure* 3). The overall summary effect measure indicated that those classified as having low skeletal muscle mass at baseline also had a lower baseline physical functioning score compared with people classified as having normal skeletal muscle mass (standardized mean difference −0.4, 95% CI −0.74, −0.05, small-moderate effect size). Statistical heterogeneity was assessed as moderate (I^2 = 66%). As three different cut points were applied across the five studies to classify participants with low or normal muscle mass, the meta-analysis was repeated with studies grouped according to cut point used (*Figure* 3A, presented in *Appendix* S2). Statistical analysis of the subgroups was not possible due to the small number of studies[35]; however, the visual assessment of the forest plots did not indicate there was evidence of systematic bias (*Figure* 3A). In the study by Daly *et al.*[41] (*n* = 428), physical function domain scores were mean dichotomized for

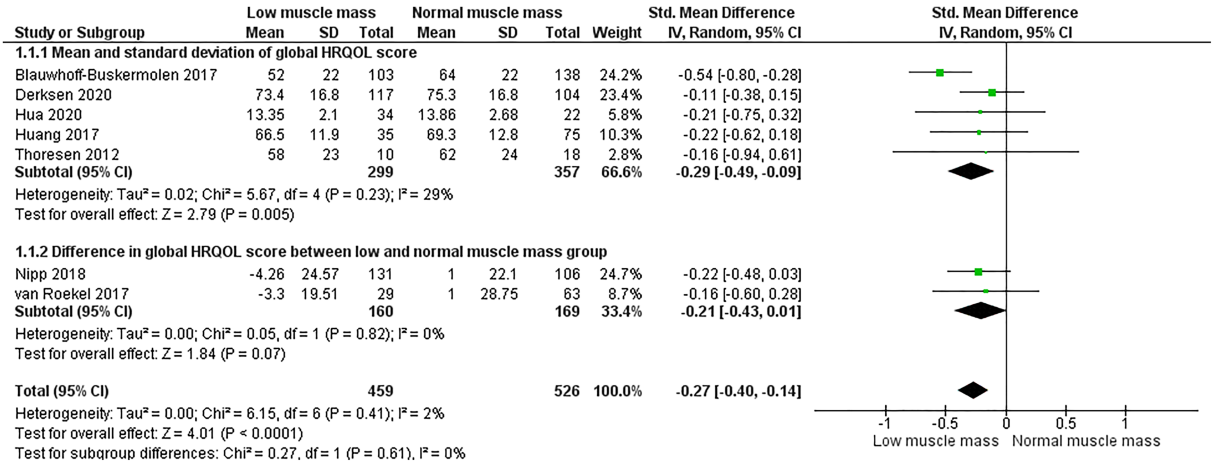

Figure 2 Meta-analysis of baseline global HRQOL scores, with participants grouped according to low or normal skeletal muscle mass stores. The five studies in first subgroup reported only univariate data without adjustment for confounding factors. The two studies in the second subgroup reported multivariate data. Cross-sectional area of skeletal muscle was measured at the third lumbar vertebra (L3) in all but two studies, where L3 measurements were imputed from alternate sites of analysis: third cervical vertebra (C3) in the study by Hua *et al*.[44] and fourth thoracic vertebra (T4) in 36% of participants in the study by Blauwhoff-Buskermolen *et al*.[40] As the choice of cut point used to detect low or normal muscle mass affects the classification of participants, a second forest plot was generated to demonstrate the pooled results of studies grouped by cut point, presented in *Appendix* S2. 'Total' refers to sample size of low or normal skeletal muscle mass groups in each study. CI, confidence interval.

logistic regression analysis and were therefore not included in the meta-analysis. Univariate analysis in that study showed low SMI was associated with poorer physical functioning [odds ratio (OR), 1.72; 95% CI, 1.27–2.33; $P < 0.001$]. After multivariate assessment [controlling for weight loss, performance status (ECOG-PS), inflammation (mGPS), and low skeletal muscle radiodensity], low SMI was no longer associated with poorer physical functioning (OR, 1.14; 95% CI, 0.74–1.73; $P = 0.555$).

A subset of included studies reported on the relationship of other domains of HRQOL with either low or normal skeletal muscle mass.[42,44,45,48,49] Meta-analysis was used to assess the difference in HRQOL for the domains of social, role, emotional, and cognitive functioning, with no significant associations found (summarized in *Table* 5). Forest plots for these meta-analyses are presented in *Appendix S3*. The study by Mitsui *et al*.[46] assessed the relationship between low or normal skeletal muscle mass with domains of HRQOL that are specific to prostate cancer treatment[53] and was therefore not included in a meta-analysis; this study found no significant differences in any of these domains (urinary, bowel, sexual, and hormonal) between low (n = 91) and normal (n = 210) skeletal muscle mass groups at baseline (all $P > 0.05$).

Five included studies reported on the relationship between skeletal muscle mass as a continuous variable and different domains of HRQOL at baseline[27,39,41–43] (*Table* 4). Three studies reported only weak or negligible correlations between SMI and HRQOL scores in all domains of the EORTC QLQ-C30.[41–43] This weak correlation was statistically significant for the physical function domain in two studies; the association was positive in one study and negative in the other.[41,43] SMI was reported to be weakly and negatively associated with social function domains scores in the study by Daly *et al*.,[41] and very weakly and negatively associated with emotional function domain scores in the study by Derksen *et al*.[42] The study by Bye *et al*.[27] reported a significant association between SMI and the physical and role functioning domains of the EORTC QLQ-C30 for both genders in both univariate analysis and after adjusting for age and tumour stage; consistent with their global HRQOL findings, scores in these domains began to decline once SMI dropped below a threshold of 42–45 cm^2/m^2 in male patients, and additionally in female patients at 37–40 cm^2/m^2. In the study by Aleixo *et al*.,[39] HRQOL in the physical function domain was significantly associated with SMI; however, in contrast with the overall results of the meta-analysis presented in *Figure* 3, this study indicated an inverse relationship (univariate analysis $\beta - 0.63$, $P = 0.02$).

Association between changes in skeletal muscle and HRQOL over time

Derksen *et al*.[42] undertook a secondary analysis to assess the association between changes in skeletal muscle mass [categorized as follows: loss (>2% decrease), stable (≤2% decrease to ≤2% gain), or gain (>2% increase)] from baseline to first progression of disease (PD1), with changes in HRQOL. Compared with the group experiencing muscle mass loss, a clinically relevant increase in global HRQOL scores was associated with the group experiencing stable muscle mass (β 9.9, 95% CI 2.4, 17.5, $P < 0.05$) and the group experiencing gain in muscle mass (β 14.7, 95% CI 8.0, 21.4, $P < 0.05$), in a multivariable linear regression analysis adjusted for several important confounding factors such as: age, gender, time to

Table 4 Relationship between skeletal muscle mass as a continuous variable, and HRQOL scores (global and domains), at baseline

Author (year)	Sample size[a](% of whole study)	Cancer type/s Stage	Treatment status at point of CT imaging	Timing of HRQOL assessments	HRQOL domain	Coefficient Univariate analysis	*P* value	Adjusted for confounders	Coefficient Multivariate analysis	*P* value
Aleixo *et al*. (2020)[39]	99 (100)	Breast Stages 0–III	Pre-chemotherapy Unclear surgical status	Baseline only (pre-chemotherapy)	Global Physical function Social/family Emotional Functional	*Linear regression* −0.12 −0.63 −0.27 −0.006 −0.19	0.052 0.002 0.16 0.98 0.18	Unadjusted		
Daly *et al*. (2020)[41]	428 (41.7)	Gastrointestinal Lung Other Stages III–IV Incurable	81% receiving active palliative chemotherapy Unclear treatment and surgical status	Baseline only (within 12 weeks of CT)	Global Physical function Role Emotional Cognitive Social	*Spearman* −0.052 −0.164 −0.070 −0.078 −0.026 −0.104	0.282 0.001 0.149 0.103 0.592 0.034	Unadjusted		
Derksen *et al*. (2020)[42]	221 (100)	Colorectal Stage IV Unresectable	Post-chemotherapy treatment Prior surgical resection in unspecified number of participants	Baseline (enrolment) Every 9 weeks until PD1	Global Physical domain Role domain Emotional domain Cognitive Social	*Pearson* 0.089 0.098 0.002 −0.006 0.091 0.035	0.19 0.15 0.97 0.02 0.18 0.61	Unadjusted[b]		
Gigic *et al*. (2020)[43]	138 (100)	Colorectal Stages I–IV Resectable	Prior chemotherapy in 53 (38%) participants Pre-surgery	Pre-surgery (baseline) 6 and 12 months post-surgery	Global Physical domain Role Social	*Spearman* 0.03 0.19 0.07 −0.06	0.68 0.02 0.42 0.52	Age Gender Tumour stage Tumour site Neoadjuvant treatment Baseline HRQOL	*Linear regression* −0.19 0.18 −0.27 0.12	0.50 0.44 0.47 0.72
Bye *et al*. (2017)[27]	734 (100)	Lung Stages IIIB–IV Incurable	Pre-chemotherapy Unclear surgical status	Baseline only (pre-chemotherapy)	Global Males Females Physical domain Males Females Role domain Males Females	*Linear regression: flexible non-linear modelling with restricted cubic splines*	0.001 0.15 0.016 0.004 0.02 0.012	Age Tumour stage	*Linear regression: flexible non-linear modelling with restricted cubic splines*	All significant associations in univariate analysis remained significant ($P < 0.05$) Individual *P* values not reported

[a]Sample size: number of participants included in analysis of relationship between skeletal muscle mass and HRQOL.
[b]Data in original study were adjusted for multiple cofounders; data supplied for this review are unadjusted.
HRQOL, health-related quality of life; PD1, first progression of disease.

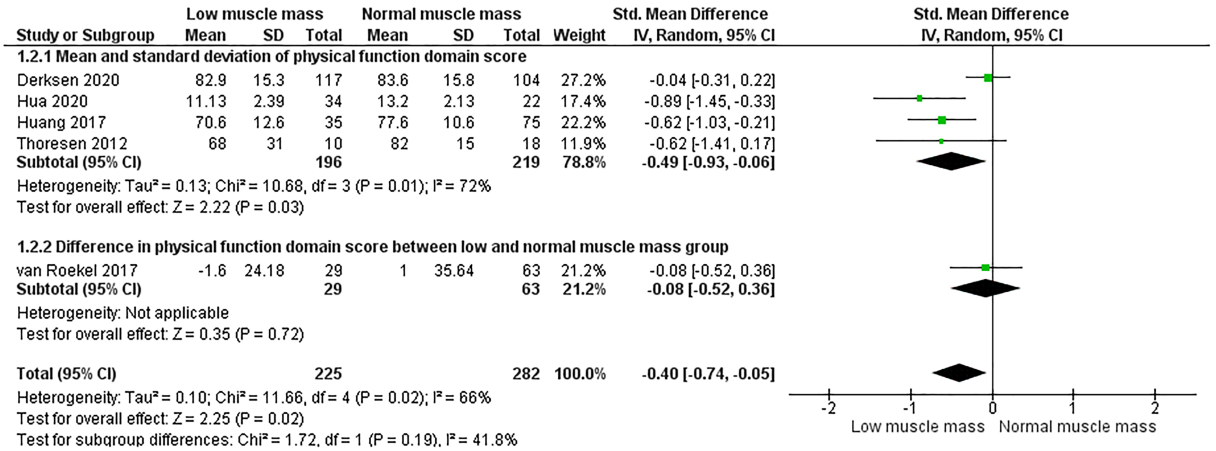

Figure 3 Meta-analysis of HRQOL physical function domain scores, with participants grouped according to low or normal skeletal muscle mass stores. The four studies in first subgroup reported only univariate data without adjustment for confounding factors. The study in the second subgroup reported multivariate data. Cross-sectional area of skeletal muscle was measured at the third lumbar vertebra (L3) in all studies excluding Hua *et al.*,[44] where L3 measurements were imputed from analysis of imaging at the third cervical vertebra (C3). As the choice of cut point used to detect low or normal muscle mass affects the classification of participants, a second forest plot was generated to demonstrate the pooled results of studies grouped by cut point, presented in *Appendix* S2. 'Total' refers to sample size of low or normal skeletal muscle mass groups in each study.

Table 5 Meta-analysis of relationship between SMI and domains of HRQOL: summary of findings

Domain	Study	Standardized mean difference between low and normal skeletal muscle mass
Social functioning	Five studies[42,44,45,48,49]	n = 507, −0.06, 95% CI −0.24, 0.12, P = 0.53, I^2 0%
Role functioning	Four studies[42,45,48,49]	n = 451, −0.25, 95% CI −0.63, 0.13, P = 0.20, I^2 67%
Emotional functioning	Three studies[42,45,48]	n = 359, −0.11, 95% CI −0.33, 0.10, P = 0.29, I^2 0%
Cognitive functioning	Three studies[42,45,48]	n = 359, −0.07, 95% CI −0.28, 0.15, P = 0.54, I^2 0%

CI, confidence interval; HRQOL, health-related quality of life; SMI, skeletal muscle index.

PD1, and previous adjuvant chemotherapy. Clinically relevant association with increased role functioning scores was also found in participants with stable muscle mass (β 12.0, 95% CI 2.2, 21.7, $P < 0.05$) or gain in muscle mass (β 17.9, 95% CI 9.4, 26.5, $P < 0.05$). Within group analysis based on cancer treatment protocols indicated that the type of treatment protocol may be a confounding factor.

Wang *et al.*[50] found that loss in total psoas muscle CSA from pre-treatment to 3-month follow up was correlated with decline in domain scores for activity (r −0.399, P = 0.019), recreation/entertainment (r −0.438, P = 0.0096), and swallowing (r −0.401, P = 0.019) (University of Washington Quality of Life[58] tool) and in the emotion domain of the University of Michigan Head and Neck Quality of Life tool (UM HNQOL[57]) (r − 0.453, P = 0.007).

Association between skeletal muscle radiodensity and baseline HRQOL

Four studies investigated the relationship between skeletal muscle radiodensity and HRQOL.[27,39,41,49] Two studies found no association.[39,49] Conversely, a large study of 734 participants[27] demonstrated that skeletal muscle radiodensity was negatively associated with physical functioning (P_{male} = 0.015, $P_{female} < 0.001$), and this remained for female patients only, after adjustment for age and stage of disease (P_{male} = 0.053, P_{female} = 0.002); in this non-linear association, HRQOL scores declined after skeletal muscle radiodensity reached a breakpoint of 32–34 HU in both genders. A study of 428 participants with mixed cancer types also showed that lower skeletal muscle radiodensity was associated with worse physical functioning on both univariate analysis (OR 2.31, 95% CI 1.69, 3.19, $P < 0.001$) and on multivariate analysis after controlling for weight loss, performance status (ECOG-PS), inflammation (mGPS), and low SMI (OR 1.67, 95% CI 1.09, 2.56, P = 0.018).[41]

Discussion

This systematic review has summarized and synthesized the literature on the relationship between CT-derived assessment of skeletal muscle mass and HRQOL in adults with cancer. In the majority of studies, this analysis was conducted using dichotomization of participants according to skeletal muscle mass status. Meta-analysis of these studies showed

that adults with low skeletal muscle mass have lower scores of HRQOL (global and physical function domains) compared with those who have normal skeletal muscle mass. A limitation of the evidence-base is that different cut points were applied between studies for the classification of skeletal muscle status that limits the robustness of these analyses and highlights the importance of making individual level data available for reanalysis of data. A subset of studies examined the correlation between skeletal muscle mass across the continuum of values, and HRQOL scores, and found little evidence of an association unless non-linear analysis was used. We also found that there is a dearth of prospective longitudinal studies examining the change in skeletal muscle mass and the relationship with HRQOL during cancer treatment.

The results of the current meta-analyses in which low SMI was associated with worse global and physical functioning HRQOL scores (*Figures* 2 and 3) may reflect a multifactorial and bidirectional relationship between skeletal muscle status and wellbeing. Reduction in skeletal muscle mass is known to contribute to decline in physical strength,[66,67] and there is evidence of a link between strength and HRQOL in cancer patients.[68,69] Skeletal muscle radiodensity, considered to be a measure of fatty infiltration of muscle, is also linked to muscle strength and function[17,70]; this was reflected in the studies by Bye *et al*.[27] and Daly *et al*.,[41] in which reduced skeletal muscle radiodensity was associated with worse physical functioning HRQOL domain scores. Conversely, reduced HRQOL associated with side effects of cancer treatment, recovery from surgery, and/or the emotional burden of having a life-threatening disease[20] may feasibly reduce an individual's engagement in usual daily routine and result in physical inactivity, which is known to be a key contributing factor to muscle wasting.[67,71] Four studies included in this review did report measures of muscle strength[40,45,47,49] and one included measures of physical performance (muscle function)[39] among their outcomes; however, no studies conducted an analysis of the relationship between muscle strength or function and HRQOL scores. This highlights the need for further exploration of the impact of muscle mass in addition to muscle strength or function on HRQOL in cancer, in order to better understand this relationship.

Interpretation of the results of this study is complicated by the inability to determine the cause of muscle mass loss. In addition to occurring as part of the ageing process,[72] skeletal muscle stores are readily depleted by illness,[73] injury,[74] and malnutrition,[75] with tumour type also influencing the degree of wasting[29]; contributions of each factor to a patient's muscle stores at the point of analysis are difficult to establish. Skeletal muscle mass and quality also deteriorate during chemotherapy treatment through a range of molecular pathways.[76,77] Most included studies did not report on participants' status of cancer treatment (medical or surgical) at the point of CT imaging, or statistically adjust for important confounding factors. In the studies where treatment status was clearly described, there was significant variation between studies.[40,43,50] This review highlights that a limitation of the evidence-base is the insufficient description of treatment status at the point of body composition assessment, and multivariate adjustment for treatment and other confounding factors. Further studies employing multivariate analysis, controlling for variables known to influence both muscle mass and/or HRQOL, are needed.

The meta-analysed primary outcome data in this review incorporated five different skeletal muscle cut points across seven studies; the potential for classification error in this sample is a major limitation, and the evidence-base would benefit from a more consistent approach to classifying low muscle mass. Published thresholds for determination of suboptimal skeletal muscle stores are influenced by the phenotypic profile of participants such as ethnicity,[78] tumour type,[29] and gender,[3] and it is important that as far as possible, authors select appropriate cut points for their own population. The use of different cut points can affect the prevalence of low muscle mass identified in a cohort[79,80] which must be taken into consideration when interpreting the results of these meta-analyses. While it has been demonstrated the association to reduced survival outcomes is consistent regardless of cut point used,[81] it remains possible that for the studies included in this review, findings in relation to HRQOL are influenced by the choice of cut point, as none of the thresholds used for low muscle mass detection were established with HRQOL as the dependant variable. The results of this study also indicate that when skeletal muscle is analysed as a continuous variable rather than categorical, there is a less clear relationship with HRQOL. It is possible that without identifying a threshold for skeletal muscle mass below which health outcomes are known to be worse,[1,3] it is difficult to elucidate the impact that incremental variations in skeletal muscle mass have on HRQOL scores using linear correlation or regression models, especially where muscle mass stores are not extremely low or high. The visual depiction of the non-linear relationship between these variables in the study by Bye *et al*.[27] reveals the skeletal muscle mass threshold below which HRQOL scores begin to decline; interestingly, these breakpoints are similar to the survival based cut points used to dichotomize participants for one or both genders, in the majority of studies included in this review, which supports the findings of the meta-analyses.[28,40–42,44,46–49]

There are additional limitations to consider in the synthesis and interpretation of the findings of this review. Seven different HRQOL assessment tools were utilized across the 14 included studies, resulting in the incompatibility of some HRQOL data for inclusion in a meta-analysis. There was also some heterogeneity in the measurement of skeletal muscle mass from CT imaging analysis. One study[50] measured the longitudinal change in CSA of a single abdominal muscle only

(psoas), a convenient but unvalidated measure that is less sensitive to change in skeletal muscle mass than total muscle CSA,[82] and two studies[40,44] obtained skeletal muscle CSA from non-lumbar imaging sites which have not been validated. Hua *et al*.[44] imputed lumbar (L3) skeletal muscle area from measurements at the third cervical vertebra (C3) using a predictive equation reported to demonstrate strong correlation to L3 measurements,[51] and Blauwhoff-Buskermolen *et al*.[40] measured CSA at the fourth thoracic vertebra (T4) in 36% of their participants with lung cancer. Additionally, while data for all but four studies were collected prospectively,[39,44,46,49] the requirement for researchers to obtain routinely conducted CT imaging for assessment at a time point appropriate to answer their research question limited the number of participants eligible for inclusion, and created an element of bias in participant selection in all studies. Four studies attempted to address this by investigating between-group differences in characteristics of participants who were included, compared with those not included based on availability of CT scans.[27,28,39,49] All four studies found at least one variable difference in the final cohort compared with those excluded; religion,[28] age,[39] disease stage and performance status,[27] and the number of comorbidities, education level, and proportion of individuals receiving chemotherapy treatment.[49] These factors may have varying impacts on the outcomes reported, and demonstrate the way in which collection of body composition data through convenience sampling limits the generalisability of results.

Future research should be directed at studies with a more consistent approach to HRQOL assessment, muscle mass stratification, and multivariate adjustment for important confounding factors. Given the body of literature synthesized in this review, use of the EORTC QLQ-C30 or FACT-G tools for HRQOL assessment would enable data comparison with the pre-existing evidence-base. Incorporation of muscle strength and function assessment into studies investigating CT-derived skeletal muscle mass or radiodensity and its impact on HRQOL could allow for more robust exploration of the significant findings in our study. There is also a need for further longitudinal research in which both body composition analysis and HRQOL assessment are undertaken concurrently and repeatedly (pre-treatment and post-treatment), with clear description of both treatment and nutrition status, to better understand the interrelationship between body composition and HRQOL in the context of cancer treatment. Attenuation of muscle mass loss through exercise, nutrition, and/or pharmaceuticals is emerging as an exciting prospect warranting further exploration[29,83]; with prevalence of low muscle mass in this review between 30% and 61% at a range of time points including pre-treatment, it would be of benefit to commence any intervention as early as possible following cancer diagnosis. Future studies will be needed to determine the subsequent impact of these interventions on HRQOL. Furthermore, our understanding of the clinical significance of changes in HRQOL scores will be enhanced by the ongoing work to understand minimally important difference.[84]

The results of this systematic review and meta-analysis suggest that suboptimal skeletal muscle mass may be linked to lower levels of HRQOL in adults with cancer. The interpretation of this relationship is limited by the varied classification of low muscle mass between studies. There is a need for prospective, longitudinal studies examining the interplay between skeletal muscle mass and HRQOL over time, and data should be made accessible to enable reanalysis according to different cut points. This review cannot determine the cause and effect relationship between these outcomes. Further exploration of this relationship through targeted research is required in order to prioritize and develop interventions for optimization of skeletal muscle status, to bring about meaningful HRQOL outcomes for patients. Conversely, interventions targeting other determinants of declining HRQOL might also impact favourably on skeletal muscle mass, indicating that skeletal muscle mass should be assessed as an outcome in such studies.

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Conflict of interest

None declared.

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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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