



The health economics burden of sarcopenia: a systematic review

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ARTICLE INFO

Keywords:

sarcopenia
economic
systematic review

ABSTRACT

Despite of better knowledge about sarcopenia, an optimal understanding of its consequences from a public health perspective remains a challenge. Specifically, the economic burden of the illness is unclear. As a support for the public health policy makers and other health actors, our objective was to perform a systematic review of the literature comparing healthcare costs between sarcopenic and non-sarcopenic patients (under the registration number CRD42018099291). A search for relevant articles was conducted on the Medline and Scopus databases. Rigorous eligibility criteria were established (e.g., subjects with sarcopenia, both men and women, mean age of the sarcopenic population) and applied by two investigators to identify suitable studies. The first screening phase, performed by 2 independent reviewers, covered 455 references. Fourteen relevant studies were included in the final analysis. Overall, we noted an important heterogeneity between studies in the way of assessing sarcopenia (i.e. operational definitions, tools and cut-offs used). There were also large variations between studies in their cost analysis settings (i.e., discrepancies in time horizon, types and sources of economic data). Most of the studies focused on hospitalization costs following surgery for a specific disease such as cancer. Finally, 11 out of the 14 studies reported higher healthcare costs for sarcopenic patients. However, most of the included studies have important methodological bias (e.g. potential confusion factors rarely taken into account), and low to moderate quality scores. More standardized research, taking into account all the limitations of the published studies, should be conducted to assess the true impact of sarcopenia on healthcare consumption.

1. Introduction

Sarcopenia, defined as a loss of muscle mass and function, is increasingly considered to be a major public health problem in the older population and in a range of clinical settings [1,2]. Indeed, the health consequences of sarcopenia include death, falls, new or prolonged hospitalizations, fractures, loss of mobility and physical function, a reduced quality of life [3–6]. Interestingly, most of these outcomes have potential direct or indirect costs, both for the patient and the society. If a lot of studies assessing the clinical outcomes of sarcopenia have been published, far less studies assessing the costs of sarcopenia are available. The economic burden-of-illness due to its engendered costs is acutely under-explored but however essential for public health policies makers. At the population level, probably the most cited paper on the economic burden of sarcopenia suggested that, in the United States, the direct health care cost attributable to this disease was estimated, for the year 2000, at \$18.5 billion (i.e. 1.5% of the total healthcare expenditure) [7]. It should be acknowledged that, in this particular study, no direct individual assessment of healthcare costs was made. However,

since a couple of years, some studies have been published to assess, at the individual level, the economic burden of sarcopenia.

The objective of the present paper is then to summarize, through a systematic review of the literature, all available information in observational studies regarding the healthcare costs of sarcopenia compared to those of individuals without the disease.

2. Methods

The research protocol has been published in July 2018 in PROSPERO under the registration number CRD42018099291 (https://www.crd.york.ac.uk/prospero/export_record_pdf.php).

For the present analysis, the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement has been rigorously followed through all steps of the research [8]. Our issue of interest was first correctly identified and defined using the following PICOS strategy: Population or disease – sarcopenic subjects; Intervention – not applicable; Comparator – subjects without sarcopenia if studied; Outcomes – health care costs; Study design - observational.

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<https://doi.org/10.1016/j.maturitas.2018.11.003>

Received 25 October 2018; Accepted 8 November 2018

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Table 1
Search strategy applied on Medline (via Ovid).

1 SARCOOPENIA/
2 sarcopenia.ti,ab,kf.
3 1 or 2
4 Health Care Costs/
5 costs.ti,ab,kf.
6 Health Expenditures/
7 expense*.ti,ab,kf.
8 expenditure*.ti,ab,kf.
9 payment*.ti,ab,kf.
10 out-of-pocket.ti,ab,kf.
11 (care adj2 consumption).ti,ab,kf.
12 economic*.ti,ab,kf.
13 "cost of illness".ti,ab,kf.
14 budget*.ti,ab,kf.
15 monetary.ti,ab,kf.
16 ((resource* or drug*) adj2 (utili?ation or allocat* or use*)).ti,ab,kf.
17 ((health or healthcare or direct service* or indirect service* or hospital* or drug*) adj2 (cost or use* or utili?ation or resource* or consumption)).ti,ab,kf.
18 financial.ti,ab,kf.
19 reimbursement.ti,ab,kf.
20 ((health* or care) adj2 service).ti,ab,kf.
21 (burden adj2 (illness or disease* or health*)).ti,ab,kf.
22 "informal care".ti,ab,kf.
23 ((patient or societal or health or institutional) adj2 perspective).ti,ab,kf.
24 (cost* adj2 analys*).ti,ab,kf.
25 "cost effective".ti,ab,kf.
26 "health policy".ti,ab,kf.
27 qalys.ti,ab,kf.
28 dalys.ti,ab,kf.
29 "quality-adjusted life years".ti,ab,kf.
30 "disability-adjusted life years".ti,ab,kf.
31 or/4-30
32 and/3,31

2.1. Literature search

The electronic databases MEDLINE (via Ovid) and Scopus were searched on May 2018 for cross-sectional, prospective and case-control studies, published in English or in French, reporting on an economic analysis (i.e., monetary value) in sarcopenic individuals. No date limitation was applied. The search strategy (applied on MEDLINE, via Ovid) and search terms, both indexed and free text, used for this research are detailed through [Table 1](#). Additional relevant studies were identified through a manual search of the bibliographic references of relevant articles and existing reviews.

2.2. Study selection

In the initial screening stage, two investigators independently reviewed the title and abstract of each of the references to exclude articles irrelevant to the systematic review, according to predefined inclusion criteria ([Table 2](#)). In the second step, the two investigators independently read the full texts of the articles that were not excluded in the initial stage and relevant selected studies that truly met all the inclusion criteria. If there was any doubt or discrepancies about the inclusion of an article, the final decision was undertaken through discussion and when needed, through the intervention of a third reviewer.

Table 2
Inclusion criteria.

Design	Cross-sectional studies, prospective studies and case-control studies.
Participants	Subjects with sarcopenia, both men and women, mean age of a sarcopenic population, no restriction regarding ethnicity or living environment (i.e., community-dwelling, institutionalized, hospitalized).
Diagnosis of sarcopenia	Any diagnosis criteria
Outcome	Health care costs/expenditures: expenditure on health care to be expressed in terms of monetary units, regardless of the manner by which it has been reported (e.g. based on care certificates, questionnaires, self-reports, medical records, etc.).
Language	French or English

2.3. Data extraction

Data were extracted by one reviewer according to a standardized data extraction form, previously pre-tested on a sample of 3 studies. All extracted data were double checked by the second reviewer and any differences in point of view were discussed in order to achieve consensus. The following data were extracted: authors; journal name; year of publication; country; objective of the study; socio-demographic data (country, type of population, sex ratio, mean age); sample size; design (number of groups, description of groups); tools and cut-offs used to assess sarcopenia (muscle mass, muscle strength and physical performance); health economic outcome(s) in monetary value; source and method of data collection ; perspective of cost ; time horizon of cost data collection ; adjustment factors ; conclusion; potential conflicts of interest and funding. When data of interest were missing, we systematically contacted authors or co-authors when information was missing in the full-text article.

2.4. Study quality assessment

All included studies were appraised for methodological quality by two independent reviewers using the Joanna Briggs Institute critical appraisal tools [9]. The two reviewers critically assessed the studies independently from each other, answering “Yes”, “No”, “Unclear”, or “Not applicable” to 8 questions (for cross-sectional studies), 10 questions (for case-control studies) or 11 questions (for cohort studies) about methodological main concerns. After these two independent reviews, the results were confronted and any discrepancies discussed with a third reviewer experienced in systematic reviews. Each study was displayed with its total points, and the number of “Yes” responses was summed for each study. We considered every study that met the inclusion criteria, independent of their quality.

2.5. Data synthesis

A descriptive analysis of the included studies has been performed under the format of a narrative report. Results have been structured according to a primary description of their general characteristics, followed by the evaluation of the intrinsic methodological quality of studies to conclude with a description of the cost comparison analyzes of each included references.

3. Results

3.1. Literature Search

The initial databases search yielded 450 references to systematically assess. An additional 5 studies, identified through a manual research, were also eligible. After the process of selection based on abstract and title and after on the full-text article review ([Fig. 1](#)), we finally included 14 studies assessing the difference in health care costs between individuals with or without sarcopenia [10–23]. Sixteen studies were rejected because of duplicate (n = 2) [11, 20], wrong outcomes (n = 13) [24–36] or wrong exposure factor (n = 1) [38].

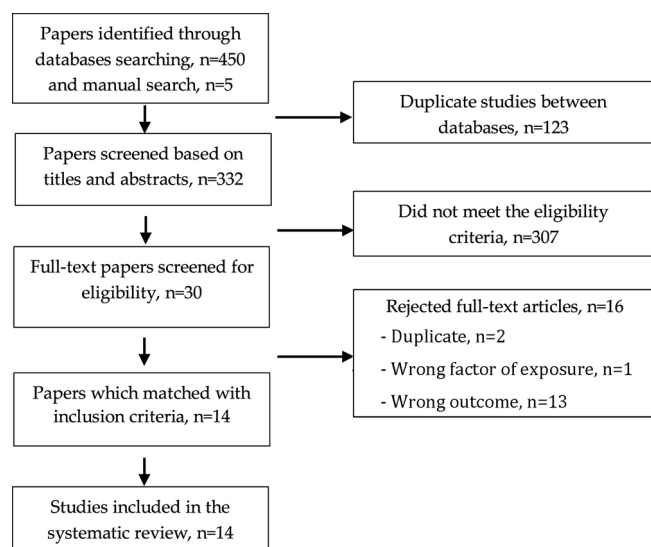


Fig. 1. Detailed literature search flow diagram.

3.2. Characteristics of the included studies

A complete presentation of the characteristics and design of the 14 included studies [10–23] is accessible in Table 3. All studies, specifically regarding their analysis of sarcopenia-related costs, followed a cross-sectional design and was comprised of 50 to 1593 participants. All were interested in both sex, with the male gender more represented (i.e., over 50% of the general population), whose median age varied from 48.5 to 83 years. The type of population studied differed a little between studies: most were carried out on hospitalized individuals (10 studies out of 14, 71%), after surgery (8 studies out of 14, 57%) or not, but two studies [17,19] related to healthy community-dwelling older adults and one to patients living in the community, but presenting a disease (i.e., cirrhosis) [22]. Regarding diagnosis of sarcopenia, only half of the included studies reported using a definition of the disease recommended by scientific societies [10,12,17–19,21,23].

The way to diagnose sarcopenia was indeed very heterogeneous, the diagnostic thresholds being also arbitrarily placed for the majority of the included studies. For instance, 11 studies out of 14 [11–18,20,22,23] applied diagnostic thresholds according to the results intrinsic to their own study and population (i.e., lowest tertile or quartile) and not based on data validated and recognized in the scientific literature, as used by the three other studies [10,19,21]. However, when applicable, the cut-offs used to measure muscle strength and physical performance were all based on more robust scientific evidence. In terms of sarcopenia costing, we observed generally fairly robust methods of data collection (i.e., use of the institution's financial accounting system). Only one study [19] collected data on the patient's self-report via a face-to-face questionnaire and four studies [12,14,17,18] did not reported at all the method of collecting cost data.

3.3. Quality assessment of the included studies

All publications included were assessed for their methodological quality by means of the Joanna Briggs Institute tool for cross-sectional studies. The scores varied from 3 to 8 points (i.e., number summed of “yes”). Even if one study [21] obtained the maximum score (8 points), the other assessed studies received a moderate-quality score (around 4 points). The details of scoring are transcribed in Table 4, but, globally, two criteria of a good methodological quality were not met for most of the researchers:

- The standardized assessment and diagnosis of the exposure (i.e.,

presence of sarcopenia or not): not met for 11 studies out of 14 [10–13,15–18,20,22,23];

- The identification and deal of confounding factors: not met for 10 out of 14 studies [10–12,14,16–20,22].

The other quality criteria (i.e., inclusion, study settings, outcome, and statistics) were usually well respected by the articles included in this analysis.

3.4. Health cost comparison between individuals with or without sarcopenia

Through Table 5, a complete picture of cost comparison analyses of the 14 included studies is available. We first noticed that the type of health care cost was diverse: some researchers were interested in the total costs during the hospital stay [10,13–16,18,21–23], others at the hospitalization cost only [12,17], and others to general health care costs for community-dwelling individuals [19,20]. Most studies reported compared costs in terms of differences in monetary value. Only one expressed this difference in percentages [10].

For the majority of studies included, we find that health care costs were significantly higher for people with sarcopenia compared to people without the disease. However, there are only two studies [13,21] which have taken into account some confounding factors, clearly recognized as having a significant impact on the consumption of health care, quite independently from the sarcopenic status, such as age, sex, number of comorbidities and nutritional status for example. Next, three studies [10,16,19] out of 14 have different conclusions: there is no significant difference in spending on health care between sarcopenic and non-sarcopenic populations (p -values > 0.05). It should also be noted that the time period during which the costs are collected in the different studies (i.e., time horizon) varied very strongly from one study to another, ranging from 7 days [16] to 8 years [17].

4. Discussion

At a first glance, from this systematic review, a trend toward an economic burden of sarcopenia is observed. However, a critical appraisal of the available data reduces the scope of the results:

- 1 Some definitions used to assess sarcopenia were not satisfactory and aligned with recent guidelines or recommendations for the operational definition of sarcopenia [39,40]. Indeed, half of the included studies only assessed muscle mass and, consequently, forgot the importance of muscle strength or physical function in sarcopenia.
- 2 Different tools are used to assess muscle mass and they do not have the same scientific value [41,42]. If, albeit not totally optimal, the DEXA is widely used and considered as the gold standard for the diagnosis of sarcopenia, the BIA is less reliable and accurate [42]. More importantly, the CT scan, used in the majority of the included studies, is still considered as a tool “under investigation” for the diagnosis of sarcopenia [42].
- 3 The cut-offs used, both for muscle mass and muscle strength, were heterogeneous. For the latter, this is not a major issue [43] since all these threshold values come from published recommendations of respectable scientific organizations [39,40,44]. The problem is more important for some cut-offs related to muscle mass assessed by CT scan that are not published or recommended by scientific societies. Two options are then available. The first is the use of threshold based on predictive value (i.e. a value below which subjects have an increased risk of adverse outcomes). These kind of cut-off, albeit not fully validated, could make sense. The second is the use of threshold based on stratification of the studied population by quartiles, tertiles of other percentiles. This is much more an issue since, in that case, the cut-off are very different from one study to another and subject considered as sarcopenic in one study could not be considered as such in the others. Unfortunately, most of the cut-off

Table 3
Characteristics of the 14 included studies.

Authors, year	Population "n" and type of population Sex ratio	Groups Definition N Age	Diagnosis of sarcopenia		Muscle strength		Physical Performance		Health care costs recording Source or method of data collection
			Definition	Muscle mass Tool Cut-off	Muscle strength Tool Cut-off	Physical Performance Tool Cut-off			
Sousa, 2016	656 hospitalized adult patients with an expected hospital stay longer than 24h 354 (53.9%) male	Two groups: Sarcopenia, n = 159, median age: 64 (IQR 19.0) years	EWGSOP	BIA SMI < 10.75 kg/m ² for men, < 6.75 kg/m ² for women	Hydraulic hand dynamometer < 30 kg for men, < 20 kg for women	Not applicable	Not reported	Discharge diagnosis-related group codes and determined on the basis of a relative weight value	
		No sarcopenia, n = 497, median age: 54 (IQR 24) years							
Huang, 2016	470 adult patients who underwent a radical gastrectomy for gastric cancer 364 (77.4%) male	Four groups: Sarcopenia, n = 47, median age: 74 (IQR 10) years	EWGSOP AWGS	CT scan L3 SMI ≤ 40.8 cm ² /m ² in men, ≤34.9 cm ² /m ² in women	Electronic hand dynamometer < 26 kg for men, < 18 kg for women	6-meter gait speed ≤0.8 m/s	Not reported	Discharge diagnosis-related group codes and determined on the basis of a relative weight value	
		Pre-sarcopenia, n = 97, median age: 65 (IQR 4) years Severe sarcopenia, n = 32, median age: 76 (IQR 9.5) years Normal, n = 294, median age: 63 (IQR 4) years							
Gani, 2016	1169 adult patients undergoing major abdominal operation 608 (52.0%) male	Two groups: Sarcopenia, n = 293, median age: 68 (IQR 59-75) years No sarcopenia, n = 876, median age: 60 (IQR 50-68) years	/	CT scan Lowest sex-specific quartile for L3 total psoas volume	/	/	Institutional cost accounting system.	Discharge diagnosis-related group codes and determined on the basis of a relative weight value	
		Sarcopenia, n = 330, 65-69 years: 22.1% / 70-74 years 33.0%, 75-79 years 23.6%, > 80 years: 21.2% No sarcopenia, n = 1007, 65-69 years: 44.8% / 70-74 years 33.9%, 75-79 years 15.4%, > 80 years: 5.96%							
Lo, 2017	1337 healthy Taiwanese people aged 65 years and older 689 (51.5%) male	Two groups: Sarcopenia, n = 330, 65-69 years: 22.1% / 70-74 years 33.0%, 75-79 years 23.6%, > 80 years: 21.2% No sarcopenia, n = 1007, 65-69 years: 44.8% / 70-74 years 33.9%, 75-79 years 15.4%, > 80 years: 5.96%	/	BIA Lowest SMI quartile: < 11.4 kg/m ² for men, < 8.5 kg/m ² for women	/	/	National Health Institute research database	Discharge diagnosis-related group codes and determined on the basis of a relative weight value	
		Sarcopenia only, n = 167, median age: 75 (IQR 69-83) years Osteopenia only, n = 48, median age: 78.5 (IQR 72-83) years Both sarcopenia and osteopenia, n = 74, median age: 83 (IQR 75-89) years No sarcopenia or osteopenia, n = 161,							
Kaplan, 2016	450 patients aged 65 years and older admitted to an intensive care unit 269 (59.8%) male	Four groups: Sarcopenia only, n = 167, median age: 75 (IQR 69-83) years Osteopenia only, n = 48, median age: 78.5 (IQR 72-83) years Both sarcopenia and osteopenia, n = 74, median age: 83 (IQR 75-89) years No sarcopenia or osteopenia, n = 161,	/	CT scan L3 SMI ≤ 52.4 cm ² /m ² in men and ≤38.5 cm ² /m ² in women	/	/	Institution's finance office	Discharge diagnosis-related group codes and determined on the basis of a relative weight value	
		Sarcopenia only, n = 167, median age: 75 (IQR 69-83) years Osteopenia only, n = 48, median age: 78.5 (IQR 72-83) years Both sarcopenia and osteopenia, n = 74, median age: 83 (IQR 75-89) years No sarcopenia or osteopenia, n = 161,							

(continued on next page)

Table 3 (continued)

Authors, year	Population “n” and type of population Sex ratio	Groups Definition N Age	Diagnosis of sarcopenia		Definition	Muscle mass		Muscle strength		Physical Performance Tool Cut-off	Health care costs recording Source or method of data collection
			Muscle mass Tool Cut-off	Definition		Muscle mass Tool Cut-off	Muscle strength Tool Cut-off				
Lou, 2017	206 overweight and obese gastric cancer patients who underwent surgery 161 (78.2%) male	Two groups: Sarcopenia, n = 14, median age: 74.8 (IQR 5.1) years No sarcopenia, n = 192, median age: 63.3 (IQR 9.93) years	EWGSOP AWGS	CT scan L3 SMI ≤ 40.8 cm ² /m ² in men, ≤ 34.9 cm ² /m ² in women	Electronic hand dynamometer < 26 kg for men, < 18 kg for women	6-meter gait speed ≤ 0.8 m/s	Not reported				
Wang, 2016	255 patients with gastric cancer who underwent curative gastrectomy 190 (74.5%) male	Two groups: Sarcopenia, n = 32, median age: 74.7 (IQR 6.8) years No sarcopenia, n = 223, median age: 63.8 (10.7) years	EWGSOP AWGS	CT scan L3 SMI ≤ 36.0 cm ² /m ² in men, ≤ 29.0 cm ² /m ² in women	Electronic hand dynamometer < 26 kg for men, < 18 kg for women	6-meter gait speed ≤ 0.8 m/s	Not reported				
Kirk, 2015	1279 patients undergoing elective major general or vascular surgery 51.3% of male in sarcopenic patients, 51.2% of mal in non-sarcopenic patients	Two groups: Sarcopenia, n = not reported, median age: 66.1 (IQR 14.0) years No sarcopenia, n = not reported, median age: 49.8 (13.9) years	/	CT scan L4 SMI < to the first tertile	/	/	Internal cost-accounting database				
Sheetz, 2013	1593 patients undergoing elective major general or vascular surgery 52.3% of male in sarcopenic patients, 52.4% of mal in non-sarcopenic patients	Two groups: Sarcopenia, n = not reported, median age: 64.4 (IQR 14.4) years No sarcopenia, n = not reported, median age: 48.5 (14.8) years	/	CT scan L4 SMI < first tertile	/	/	Internal cost-accounting database				
Antunes, 2017	201 hospitalised older adults 66.7% of male in sarcopenic patients, 37.8% of mal in non-sarcopenic patients	Two groups: Sarcopenia, n = 21, > 75 years: 2(9.5%), ≤ 75 years: 19 (90.5%) No sarcopenia, n = 180, > 75 years: 74(41.1%), ≤ 75 years: 106 (58.9%)	EWGSOP	Mid-arm circumference, triceps skin-fold thickness ≤ 2 standard deviations from the mean value of the muscle mass of young adults of the same gender and ethnic group	Handheld grip ≤ 29 kg and BMI ≤ 24 kg/m ² , ≤ 30 and BMI between 24.1 and 28 kg/m ² , ≤ 32 and BMI > 28 kg/m ² for men, ≤ 17 kg and BMI ≤ 24 kg/m ² , ≤ 17.3 kg and BMI between 24.1 and 26 kg/m ² , ≤ 18 kg and BMI between 26.1 and 29 kg/m ² , ≤ 21 and BMI > 29 kg/m ² for women	Time Up and Go test > 20 seconds	Patients' destination and diagnosis related group code after patients discharge.				
Bokshan, 2017	50 patients older than 55 years having undergone thoracolumbar decompression 8 (50.0%) male in sarcopenic patients, 18 (52.9%) male in non-sarcopenic patients	Two groups: Sarcopenia, n = 16, mean age : 76.6 (SD 2.2) years No sarcopenia, n = 34, 70.8 (SD 1.4) years	/	CT scan Total psoas area < sex-specific lowest tertile	/	/	Hospital charge centre				
Chen, 2018	185 patients aged over 18 who underwent colorectal surgery for cancer	Two groups: Sarcopenia, n = 51, mean age: 70.7 (SD 12.6)	EWGSOP	CT scan L3 SMI ≤ 40.8 cm ² /m ² in men, ≤ 34.9 cm ² /m ² in women	Handheld dynamometer < 26 kg for men, < 18 kg for women	6-meter gait speed ≤ 0.8 m/s	Not reported				

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Table 3 (continued)

Authors, year	Population “n” and type of population Sex ratio	Groups		Definition	Diagnosis of sarcopenia		Muscle strength Tool Cut-off	Physical Performance Tool Cut-off	Health care costs recording Source or method of data collection
		Definition N	Age		Muscle mass Tool Cut-off	Muscle mass Tool Cut-off			
Mijnarends, 2016	34 (66.7%) male in sarcopenic patients, 90 (67.2%) male in non sarcopenic patients 227 community-dwelling older adults 117 (51.5%) male	No sarcopenia, n = 134, mean age: 59.2 (SD 13.0)	Age	EWGSOP	BIA SMI $\leq 10,75 \text{ kg/m}^2$ in men, $\leq 6,75 \text{ kg/m}^2$ in women	Handheld dynamometer < 30 kg in men and < 20 kg in women	4-meter gait speed $\leq 0.8 \text{ m/s}$	Questionnaire (interview face- to-face) developed for this purpose.	
van Vugt, 2017	224 patients with cirrhosis listed for liver transplantation 149 (66.5%) of male	Three groups: Sarcopenia, n = 53, mean age: 80.4 (SD 7.1) years No sarcopenia, age and sex matched, n = 53, mean age: 79.7 (SD 7.0) years No sarcopenia, n = 174, mean age: 73.3 (SD 6.4) years	Two groups: Sarcopenia, n = 55, mean age: 56 (IQR 48-69) years No sarcopenia, n = 169, mean age: 56 (IQR 49-61) years	/	CT scan Total psoas area < sex-specific lowest quartile	/	/	Hospital's electronic accounting system	

* BIA = Bioelectrical Impedance Analysis; IQR = Inter Quartile Range; CT = Computed Tomography; SMI = skeletal muscle mass index; EWGSOP = European Working Group on Sarcopenia in Older People; AWGS = Asian Working group on Sarcopenia; L3 = lumbar vertebrae 3; L4 = lumbar vertebrae 4; SD = standard deviation.
 * BIA = Bioelectrical Impedance Analysis; IQR = Inter Quartile Range; CT = Computed Tomography; SMI = skeletal muscle mass index; EWGSOP = European Working Group on Sarcopenia in Older People; AWGS = Asian Working group on Sarcopenia; L4 = lumbar vertebrae 4; SD = standard deviation.

Table 4
Quality of studies (Joanna Briggs Institute - Cross-sectional studies).

Authors, year	1. Clear inclusion criteria	2. Subjects and setting described	3. Sarcopenia assessment valid and reliable	4. Standard criteria for sarcopenia	5. Confounding factors identified	6. Deal of confounding factors	7. Outcomes valid and reliable	8. Appropriate statistics	Total of yes
Sousa, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Huang, 2016	Yes	Yes	Yes	Yes	No	No	Unclear	Yes	5
Gani, 2016	No	Yes	Ni	No	Yes	Yes	Yes	Yes	5
Lo, 2017	No	Yes	Yes	No	No	No	Yes	Yes	4
Kaplan, 2016	Yes	Yes	Yes	No	No	No	Yes	Yes	4
Lou, 2017	Yes	Yes	Yes	No	No	No	Unclear	Yes	4
Wang, 2016	Yes	Yes	Yes	No	No	No	Unclear	Yes	4
Kirk, 2015	No	Yes	No	No	Unclear	Yes	Yes	Yes	4
Sheetz, 2013	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	5
Antunes, 2017	Yes	Yes	No	No	No	No	Yes	Yes	4
Bokshan, 2017	Yes	Yes	No	No	Yes	No	Yes	Yes	5
Chen, 2018	Yes	Yes	No	No	No	No	No	Yes	3
Mijnarends, 2016	Yes	Yes	Yes	Yes	Yes	No	No	Yes	6
van Vugt, 2017	Yes	Yes	No	No	No	No	Yes	Yes	4

values for CT scan are based on stratification of the studies population, making the observed results of limited interest. For BIA, one selected study also used this approach making again the interpretation quite complex.

- The populations in the selected papers were also heterogeneous but a substantial proportion included subjects experiencing major surgeries for major diseases such as cancer. Consequently, our summary results could hardly be extrapolated to older subject.
- In the majority of the included papers (12 studies out of 14, 86%), the group having sarcopenia and the group who do not were not balanced according to demographic or clinical characteristics. For example, age could be very different among groups and this is, obviously, a major confounding factors when comparing the healthcare costs between two groups. Unfortunately, adjustment for all these potential confounding variables were rarely performed in the included studies.
- The costs were, in the majority of the studies, limited to those occurred at the hospital immediately after the surgery. When having in mind the long-term potential consequences of sarcopenia on fractures, fall or loss of autonomy, the time frame and the setting is probably too limited to have a global view of the economic burden of the disease.
- At last, the quality of most of the included studies were low to moderate, and in a substantial proportion of them, few information were available regarding the collection of cost data, the confounding variables or the statistical analysis performed. It should be acknowledged that most of the papers does not have the economic burden as primary outcome and, consequently, less information were available when presenting these data.

This work of systematic review is, to our knowledge, the first carried out on this theme, but, however, presents certain limitations. First, we searched for relevant manuscripts in two databases, as recommended, but some relevant databases were not investigated (e.g. EMBASE) due to logistical constraints. However, manual search of other relevant articles were performed and we do not believe that many papers were missing. Second, we included, as discussed before, studies having used non-validated and potentially irrelevant cut-off for the assessment of muscle mass. Maybe that other studies using these kinds of cut-offs but without claiming that they diagnosed sarcopenia with it have been missed with our search strategy. Third, because of the heterogeneous nature of the selected papers, no meta-analysis has been performed and it was not possible to assess publication bias. Lastly, we decided to avoid transformation of all monetary units into a single one. It can be discussed and challenged but our idea was to avoid (by us but mostly by others) making some kind of “global summary cost of sarcopenia” that

would have been false given all limitations of the selected papers.

5. Conclusion

In conclusion, our systematic review found a large heterogeneity between studies regarding the selected population, the time horizon, the type and source of economic data but, globally, shows some trends toward a more important use of healthcare resources in the sarcopenic population. However, the heterogeneity in the tools to measure of sarcopenia, the use of non-validated thresholds to define sarcopenia, and the moderate or even poor methodological quality of most of the studies, do not allow to make definitive conclusion regarding the economic burden of sarcopenia. There is a clear need for well conducted studies in the field of sarcopenia regarding economic analysis.

Contributors

Olivier Bruyère screened the results of the search, assessed titles and abstracts for eligibility, performed full-text screening, data extraction, quality assessment and drafted the paper.

Charlotte Beaudart screened the results of the search, assessed titles and abstracts for eligibility, performed full-text screening, data extraction, quality assessment and drafted the paper.

Olivier Ethgen acted as an independent reviewer where needed.

Jean-Yves Reginster acted as an independent reviewer where needed.

Médée Locquet ran the searches, screened the results of the search, assessed titles and abstracts for eligibility, performed full-text screening, data extraction, quality assessment and drafted the paper.

All authors were responsible for the study concept and design, and participated in the development of the search strategy and the critical appraisal of the results.

They were all responsible for editing and reviewing the manuscript, and all saw approved the final version.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for the preparation of this review.

Provenance and peer review

This article has undergone peer review.

Table 5
Synthesis of cost analyses among the 14 included studies.

Authors, year	Cost 1		Cost 2		P-value	Type of health care cost	Cost for sarcopenic	Cost for non-sarcopenic	P-value	Cost for sarcopenic	Cost for non-sarcopenic	P-value	Time horizon for cost-related data collection	Adjustment factors for cost comparison analysis
	Type of health care cost	Cost for sarcopenic	Cost for non-sarcopenic	Type of health care cost										
Sousa, 2016	Median total hospital costs during hospital stay	€3151 (IQR €4175)	€2170 (IQR €2515)	< 0.001	/	/	/	/	/	/	/	/	Median days of hospital stay: Sarcopenia: 9.0 (IQR 10.0) days; No sarcopenia: 6.0 (IQR 6.0) days Not reported	Age, marital status, hospital ward, length of hospital stay, nutritional status None
Huang, 2016	Median hospital costs	¥63 995.8 (IQR ¥31 449.0)	¥54 395.3 (IQR ¥17 625.7)	0.001	/	/	/	/	/	/	/	/		
Gani, 2016	Median hospital costs (health system)	\$38,804 (IQR \$25,027-\$43,462)	(IQR \$22,573-\$38,025)	< 0.001	Median total net payments (patient)	\$37 335 (IQR \$28 640-\$55 717)	\$32,680 (IQR \$24 326-\$45 756)	< 0.001					Median days of hospital stay: whole sample: 8 (IQR 6-12)	Patient and disease characteristics (only for total hospital costs)
Lo, 2017	Median cost of hospitalisation	NT \$77 500	NT \$ 38 700	< 0.001	Median total medical expenditure	NT \$102 000	NT \$ 67 400	< 0.001					8 years	None
Kaplan, 2016	Median hospital costs	\$ 31600 (IQR \$17 100-\$57 100)	\$ 33600 (IQR \$18 500-\$62 600)	0.82	/	/	/	/	/	/	/	/	Median days of hospital stay: Sarcopenia: 7 (IQR 4-12); No sarcopenia: 7 (IQR 5-11)	None
Lou, 2017	Median hospital costs	¥68 026 (IQR ¥41 132)	¥ 55 316 (IQR 18 003)	0.003	/	/	/	/	/	/	/	/	Not reported	None
Wang, 2016	Median hospital costs	¥ 70 627 (IQR ¥29 961)	¥ 54 348 (IQR ¥ 21 181)	< 0.001	/	/	/	/	/	/	/	/	Not reported	None
Kirk, 2015	Median in-hospital costs	\$67 525	\$39 720	< 0.001									1 year	Adjusted but factors not reported
Sheetz, 2013	90-day post operation procedural costs and facility fees	\$ 34 796.37	\$ 21 380.07	< 0.001	Median hospital cost	\$ 35 056.30	\$ 18 488.48	< 0.001					From 2 days before operation to 90 days postoperatively	None
Antunes, 2017	Difference in hospital costs deviation	99% had cost deviation (superior the mean - i.e., €2 396,24)	84,4% had cost deviation (superior the mean - i.e., €2 396,24)	> 0.05	/	/	/	/	/	/	/	/	Median days of hospital stay: 8 days (IQR 8)	None
Bokshan, 2017	Median total inpatient cost	\$53 128 (SEM: ± \$10 612)	\$30 292 (SEM: ± \$6 535)	0.04	/	/	/	/	/	/	/	/	Period following spine surgery: a median of 4,6 years (IQR 6 days - 12,7 years)	None
Chen, 2018	Median hospitalization costs	¥ 52 793.4 (SD: ¥ 21 421.0)	¥ 45 347.6 (SD: ¥ 20 734.9)	0.01	/	/	/	/	/	/	/	/	30 days post-surgery	None
Mijnarends, 2016	Average costs of health care per person per 3 months	€4 325 (95%CI: €3 198-€5 471)	€2 768 (95%CI: €1 914-€3 743)	> 0.05	/	/	/	/	/	/	/	/	3 months	Sarcopenic matched for age and sex
van Vugt, 2017	Median total hospital costs	€11 294 (IQR €3570-€46 469)	€6 878 (IQR €1305-€20 683)	0.01	Median cost per day	€68 (IQR €16-€503)	€40 (IQR €10-€108)	0.01					Median days during listed for transplantation: 176 days (IQR 51-306)	None

*IQR = Inter Quartile Range; NT\$ = New Taiwan Dollar; SEM = standard error of mean; 95%CI = 95% confidence interval.

Acknowledgments

We warmly thank Dr. Teresa Amaral for providing us with additional information for a detailed analysis of her article in our systematic review.

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