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Sarcopenia as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis.

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Keywords:	Sarcopenia, All-cause mortality, Nursing Home, Meta-analysis

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3 **Sarcopenia as a predictor of all-cause mortality among older nursing home**
4 **residents: a systematic review and meta-analysis.**
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Abstract

Objective: this present study aims to review the evidence of sarcopenia as a predictor of all-cause mortality among elderly nursing home residents.

Design: systematic review and meta-analysis

Methods: Systematic review of literature and meta-analysis were performed using 3 electronic databases (PubMed, EMBASE, and the Cochrane Library) searching for studies that prospectively examined the relationship between sarcopenia and all-cause mortality among elderly nursing home residents.

Results: Of 2292 studies identified through the systematic review, six studies (1494 participants) were included in the meta-analysis. Sarcopenia was significantly associated with higher risk for all-cause mortality among elderly nursing home residents (pooled OR=1.69, 95% confidence interval [95% CI] =1.24-2.30, P=0.001).

In addition, the subgroup analysis for length of follow-up demonstrated that follow-up period 1 year or more years analysis was association with all-cause mortality (pooled HR 1.64, 95% CI 1.16-2.33, p=0.006), however, it was not found with the follow-up period less than 1 year. Similar result was also found with the number of size is greater than (or equal to) 100 (pooled OR=1.86, 95% CI=1.34-2.60).

Conclusion: sarcopenia is found to be a significant predictor of all-cause mortality among older nursing home people. Therefore, it is significant to diagnose Sarcopenia and to intervene, for the sake of reducing mortality rates in the elderly people among nursing home.

Key words: Sarcopenia; All-cause mortality; Nursing Home; Meta-analysis

Strengths and limitations of this study

1. we used an extensive search process in electronic data-base and assessed, methodological quality, and tested the heterogeneity and publication bias among the included studies.
2. This systematic review and meta-analysis assessed the overall quality of the evidence using Newcastle Ottawa Scale (NOS) approach.
3. The pooled results showed good consistency (low between-study heterogeneity), because we used same unified diagnostic criteria of Sarcopenia(EWGSOP) and the same population(nursing home resident elderly people).
4. the studies included in this analysis were insufficient and the size sample was relatively smaller.
5. language of studies was limited to English and consequently we may have missing data from important studies published in other languages, which may result in potential language bias.

1. Introduction

Sarcopenia is a common syndrome characterized by a loss of muscle mass and strength with functional impairment and adverse health outcomes due to cumulative deficits of multiple systems¹. Particularly, nursing home residents are at high risk for Sarcopenia². According to the studies, the prevalence of Sarcopenia was 1-29% for community-dwelling older adults, 14-33% in nursing homes and 10-24.3% for those in hospitals³. Sarcopenia leads to worse outcome in elderly people including physical disability, fall, fractures, poor quality of life, mortality and hospitalization⁴⁻⁶. Among these, mortality might be considered the most important outcome in elderly people. So far the relationship between mortality and operational criteria defined Sarcopenia has been well described in community-dwelling older adults and hospital patients. A recent meta-analysis study, Liu⁷*et al* analyzed the sarcopenia and mortality with the conclusion that Sarcopenia is a predictor of all-cause mortality among

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3 community-dwelling older people. However, there is no consistent conclusion
4 regarding the relationship between sarcopenia and mortality among nursing home
5 resident. It has been shown that the mortality rate in nursing home is approximately
6 eightfold higher than that in the community, therefore, it is very important to confirm
7 the risk factor for mortality among nursing home resident.
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12 Several studies found that old people with sarcopenia were predictor of all-cause
13 mortality among nursing home resident^{8,9}. However, some studies didn't find out any
14 significant relationship between sarcopenia and all-cause mortality¹⁰⁻¹³. Given the
15 observed contradictory relationship between sarcopenia and all-cause mortality
16 among nursing home resident in some studies, further studies are needed, However,
17 no systematic review of meta-analysis studies on this topic have been conducted in
18 the literature. Therefore, our study aims to identify and compare prospective cohort
19 studies examining sarcopenia as a predictor of all-cause mortality among nursing
20 home resident according to the PRISMA guidelines.
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29 **2. Materials and methods**

30 This systematic review was undertaken and reported according to the Preferred
31 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁴.
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34 **2.1. Search strategy and selection criteria**

35 A systematic literature search were conducted in PubMed, EMBASE, and
36 Cochrane CENTRAL Library Issue in November 2017. The search strategy was tailored
37 to according to each database. We used a combination of key words such as
38 mortality(mortality*), OR death(death*), OR survival(survival*) and sarcopenia
39 (sarcopenia*), as well as MeSH terms. Subject terms and truncation symbol were also
40 used in our search strategy. We searched the potential gray studies through Google
41 Scholar. Furthermore, a manual search was carried out on the references of included
42 studies.
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51 **2.2. Study selection**

52 These studies identified by our search strategy were reviewed by teams of
53 two independently blinded reviewers (Zhang XM and Wang CH) who evaluated each
54 title and abstract. In case of disagreement on inclusion or exclusion of studies, this
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3 issue was discussed and a third reviewer evaluated the study until consensus was
4 reached by the reviewers.
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6 7 **2.3. Inclusion and exclusion criteria**

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9 The following eligibility and exclusion criteria were prespecified. Studies had to
10 fulfill the following four inclusion criteria: (1) prospective cohort studies, (2) studies
11 investigating whether sarcopenia was a predictor of mortality, (3) studies reporting
12 clear diagnostic criteria for sarcopenia (4) Type of participant: elderly adult among
13 nursing home or nursing care. Exclusion criteria were as following: (1) Type of
14 participant: community-dwelling older people (aged 65 years and older) or
15 hospitalized older people; (2) article type: only abstract, letters and laboratory
16 research; review articles; (3) insufficient date; (4) other languages of studies, except
17 English.
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20 21 22 23 24 **2.4. Data extraction**

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26 Two investigators (Zhang XM, Wang CH) independently abstracted the data from
27 the selected studies using a standardized data-abstraction form. The following
28 information were extracted from included papers: author, country, year of publication,
29 demographic characteristics of participants (e.g., sample size, male proportion),
30 measurement methods of sarcopenia, follow-up period, study quality. The reviewers
31 cross-checked all extracted data. Disagreements were resolved by discussion until
32 consensus was reached.
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39 40 41 **2.5. Assessment of risk bias**

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43 Assessment of risk of bias was performed by two independent reviewers (Zhang
44 XM, Wang CH) according to the Newcastle Ottawa Scale (NOS)¹⁵: (1)
45 representativeness of the exposed cohort, (2) comparability of group, (3) blinding of
46 investigators who measured outcomes, (4) the time and completeness of follow-up, (5)
47 contamination bias, and (6) other potential sources of bias. Articles were scored as
48 follows: > 7 as high quality (NOS).
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52 53 **2.6. Statistical analysis**

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55 The STATA version 14.0 (Stata Corp, College Station, TX, USA) was
56 independently used for all analyses by two authors ((Zhang XM, Dou QL). Hazard
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3 ratios(HRs), odds ratio(OR) and their 95%CIs of mortality for sarcopenia compared
4 with non-sarcopenia were extracted from studies for future meta-analysis. Subgroup
5 analyses were conducted by sample size, follow-up period, if there was more than one
6 study in the subgroup. The statistical heterogeneity among the included studies was
7 examined with Cochran's Q statistic using chi-square and I² Statistics, and I² value of
8 25%, 50% and 75% represented the cut-off of low, moderate and high heterogeneity,
9 respectively. If heterogeneity was found to be reasonably high between studies, the
10 random effects model was used. Otherwise, the fixed effects model was used. Results
11 were illustrated using forest plots.
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19 **3. Results**

20 **3.1. Search results**

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22 The literature search strategy initially identified 2292 articles. After removal of
23 duplicates, 1965 articles were screened for potential eligibility. A total of 85
24 publications remained for further consideration after that we screened titles and
25 abstracts and removed non-relative articles. These studies were screened according to
26 the predefined inclusion and exclusion criteria for including in the meta-analysis,
27 resulting in a total of six eligible studies (Figure.1).
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34 **3.2 Included studies**

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36 Six prospective cohort studies were included in our meta-analysis with the total
37 number of 1494 participants. Study characteristics of included papers are displayed in
38 table 1. There were 2 studies conducted in Turkey^{16, 17}, 1 study in Italy¹⁸⁻²⁰, 1
39 study in Australia²¹, 1 study in Belgium, 1 study in Israel. All of the studies selected
40 all-cause mortality as the clinical outcome, and used the sarcopenia criteria of
41 EWGSOP. The EWGSOP defined sarcopenia in men as ALM adjusted for height
42 squared $\leq 7.26 \text{ kg/m}^2$ OR $\leq 5.54 \text{ kg/m}^2$ for women combined with low hand-grip
43 strength ($< 30 \text{ kg}$) and low gait speed ($< 0.8 \text{ m/s}$), and/or low grip strength $< 30 \text{ kg}$
44 for men and $< 20 \text{ kg}$ for women²². The prevalence of sarcopenia ranged from 32.8% to
45 73.3%. The largest study consisted of 662 men and women, and the smallest cohort
46 only had 58 individuals. Follow-up periods were not longer varying from 6 months to
47 24 months, and the adjusted HR were displayed in four studies, and one was used OR,
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3 the other one was RR.
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5 **3.3 Quality assessment**

6 The methodological quality evaluation using NOS was shown in Table1. The
7 score ranged from six to nine, the scores of five studies were more than seven.
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10 **3.4 Sarcopenia as a predictor of mortality**

11 **3.4.1 Meta-analysis of studies**

12 Six studies examined the association between sarcopenia and mortality among
13 nursing home resident. The pooled HR values were calculated by fixed-effects models.
14 As show in Figure2, The pooled hazard ratios (HRs) of all-cause mortality for
15 sarcopenia versus the non-sarcopenia was 1.69(95%CI=1.24-2.30,P=0.001). No
16 significant heterogeneity was observed across these studies((Q-value = 4.33, degree of
17 freedom =5,I²= 0%, p =0.503).
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25 **3.4.2 Subgroup analysis**

26 The six studies with HR of all-cause mortality risks for sarcopenia among nursing
27 home resident were further analyze by subgroup. Figure3 presents a comparison of
28 all-cause mortality risk stratified by length of follow-up for muscle mass. Two studies
29 with follow-up period less than 1year for muscle mass(pooled HR 1.85, 95%CI
30 0.95–3.60, p = 0.070); whereas the other four studies with follow-up period 1year or
31 more years analysis (pooled HR 1.64,95%CI 1.16-2.33,p=0.006). Figure 4 displays
32 comparison of all-cause mortality risk stratified by sample size which indicated the
33 number of size less 100(pooled HR 0.81,95%CI 0.33-1.98,p = 0.645), but the number
34 of size is greater than (or equal to) 100(pooled HR 1.86, 95% CI 1.34-2.60,p = 0.001).
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44 **3.4.3 publication bias assessment**

45 There was no significant publication among the studies using Begg's
46 test:P=0.260.(Figure 5)
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51 **4. Discussion**

52 In this meta-analysis, we found evidence suggesting the risk of all-cause
53 mortality among nursing resident older people with Sarcopenia was higher than that
54 among nursing resident older people without Sarcopenia. To the best of our
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3 knowledge, this is the first meta-analysis to explore the relationship between
4 Sarcopenia and all-cause mortality among nursing resident elderly people. Our study
5 indicated assessing Sarcopenia is really important among the aged that living in
6 nursing home or care.
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10 Ping Liu⁷ *et al.* implemented a systematic review and meta-analysis regarding
11 the association of sarcopenia with mortality in 2016, published in 2017. However, this
12 review including population were all involving community-dwelling older people. It
13 is quite obvious that community-dwelling older people is totally different with the
14 aged living in nursing home. Community-dwelling older people is relatively healthy,
15 well-functioning individuals than elderly people living in nursing home. So far
16 Shu-Fang Chang²³ and Beaudart²⁴ both performed a systematic review to evaluate the
17 link between Sarcopenia and all-cause mortality, however there were some
18 methodological shortcomings, such as various diagnostic criteria of Sarcopenia, crude
19 ORs as effect, various population involving community-dwelling older people,
20 hospitalized patients. Although subgroup of nursing home resident was analyze in
21 Beaudart's study, there is only two research was assessed, which maybe underestimate
22 or overestimated their result. There were six studies in our review, which only focus
23 on the association of mortality and Sarcopenia in nursing home elderly people. We
24 adopted the same diagnostic criteria of Sarcopenia(EWGSOP) and the Same type
25 population (nursing home resident elderly people) to decreased clinical heterogeneity.
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40 This meta-analysis of including six cohort studies, shows Sarcopenia is an
41 important predictor of all-cause mortality among elderly nursing home resident. The
42 pooled HR value of all-cause mortality was 1.69(95%CI=1.24-2.30, P=0.001, I² =
43 0%). The perfect I² suggesting no significant heterogeneity was showed across these
44 researches. In addition our study pooled HR value is higher than Ping Liu(1.60
45 95%CI: 1.24–2.06), the primary reason was the different type of population. The
46 aged living in nursing home usual had worse health condition that may had more
47 comorbidities, more disability and more geriatric syndromes, such as cognitive
48 dysfunction and malnutrition^{11, 25-27}. This comprehensive risk factor may aggravate
49 the process of Sarcopenia.
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3 The prevalence of Sarcopenia was 32.8-73.3% which is higher than other studies,
4 the different was mainly due to the mean age, various population and different
5 diagnostic tools, particularly the ways measure of muscle mass. Sarcopenia was
6 associated with all-cause mortality in the size of sample 100 or more numbers group,
7 but it was not significant in the size of less 100 group when subgroup was conducted
8 according to size number in this systematic review. It was known that the larger the
9 sample size, the more confident of the statistic. The subgroup of length of follow-up
10 analysis was demonstrated that follow-up period 1 year or more years analysis was
11 association with all-cause mortality (pooled HR 1.64, 95%CI 1.16-2.33, $p=0.006$),
12 however, it was not found with the follow-up period less than 1 year. The reason
13 maybe, with the time of aging, Sarcopenia will aggravatingly impact to survival of
14 patient, which may increase the rates of mortality.

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16 The underlying mechanisms between sarcopenia and a higher risk of all-cause
17 mortality did not have a conclusion, some aspects should be mentioned at least.
18 Firstly Sarcopenia is linked to multifactor ranging to aging process²⁸, multiple
19 Chronic health conditions, unhealthy lifestyle²⁹, hormonal factors³⁰, inflammation³¹
20 and so on³². In the meanwhile, the above factors are considered linked to mortality and
21 the development of multifactor worsened the situation of Sarcopenia leading to a
22 passive adaptation to adversity or external stressors, which in turn generate an increased
23 poor adverse outcomes³³. Secondly, according to the study of Fried³⁴ *et al.*, sarcopenia
24 was an critical etiological role in the frailty process, which is related, through frailty,
25 to pernicious consequences. For instance recurrent falls, bone fracture, disability,
26 multiple emergency room visits and hospital admissions, and eventually death^{35, 36}.
27 For sarcopenia is a geriatric syndrome rather than a disease, the mechanism of
28 Sarcopenia must be complex, which need more researches to explore.

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30 Our meta-analysis review has multiple strengths and some limitation. One
31 strength is we used an extensive search process in electronic data-base and assessed,
32 methodological quality, and tested the heterogeneity and publication bias among the
33 included studies. Another strength was the same unified diagnostic criteria of
34 Sarcopenia (EWGSOP) and the same population (nursing home resident elderly
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3 people) to reduce heterogeneity, and improve the research quality. There are some
4 limitations in our studies. Firstly, the studies included in this analysis were insufficient
5 and the size sample was relatively smaller. Secondly, language of studies was limited
6 to English and consequently we may have missing data from important studies
7 published in other languages, which may result in potential language bias. In addition,
8 the follow-up was relatively short for the necessary latency, which maybe
9 underestimate the results.
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16 **5. Conclusion**

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18 This study provides the evidence that sarcopenia is a significant predictor of
19 all-cause mortality among nursing home resident older people based on the
20 comprehensive systematic review and meta- Analysis. Future studies are needed to
21 provide evidence for specific interventions aimed at preventing and treating
22 Sarcopenia, which can reduce the mortality in the elderly people living in nursing
23 home.
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29 **6. Acknowledgements**

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32 hospital of Baoan ShenZhen for their guidance and support.
33

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37 not-for-profit sectors. No sponsors had any role in the design, methods, subject
38 recruitment, data collections, analysis, or preparation of this manuscript.
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41 **8. Contributors**

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43 Xiaoming Zhang was responsible for producing the initial draft of the manuscript.

44
45 Conghua Wang was responsible for data extraction and for producing the initial draft
46 of the manuscript.
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48
49 Qingli Dou was responsible for data extraction.

50
51 Wenwu Zhang was responsible for screening the papers and quality assessment.

52
53 Xiaohua Xiewas responsible for screening the papers.

54
55 Yunzhi Yang was responsible for quality assessment, statistical analysis and revision
56 of the manuscript.
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All the authors approved the final version of the manuscript

9. Conflict of Interest

None of the authors have any conflict of interest to declare.

10. Data Sharing Statements

All the data can find in the electronic databases(PubMed, EMBASE, and the Cochrane Library).

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Table 1 Summary of Included Studies on sarcopenia Associated with all-cause mortality

Author,	Country	Year	Male	Sample number	Age of patients, years	Sarcopenia Criteria	Prevalence%	Follow-up period	Outcome	Effect Measure	Adjusted Or Crude HR/OR	Quality*
Saka B	Turkey	2015	51%	402	78.0 ± 7.9	EWGSO P	73.3	12month	All-cause mortality	HR	Adjusted	8
Yalcin A	Turkey	2017	54.3%	141	79.17 ± 7.99	EWGSO P	53.9	24month	All-cause mortality	HR	Adjusted	7
Landi F	Italy	2012	25%	122	84.1 ± 4.8	EWGSO P	32.8	6month	All-cause mortality	HRs	Adjusted	9
Henwood T	Australia	2017	29.3%	58	85.7 ± 8.2	EWGSO P	51.7	18month	All-cause mortality	RR	Adjusted	6
Buckinx F	Belgium	2017	27.5%	662	83.2 ± 8.99	EWGSO P	36.2	12month	All-cause mortality	OR	Adjusted	7
Kimyagarov S	Israel	2012	41.2%	109	84.9 ± 7.4	EWGSO	40.3	12month	All-cause mortality	HR	Adjusted	7

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3 Figure 1. Search results and study selection.

4 Figure 2. Meta-analysis of the association between Sarcopenia and mortality among older nursing
5 home residents.

6 Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up.

7 Figure 4. Subgroup analyses of the meta-analysis according to the sample size.

8 Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents.
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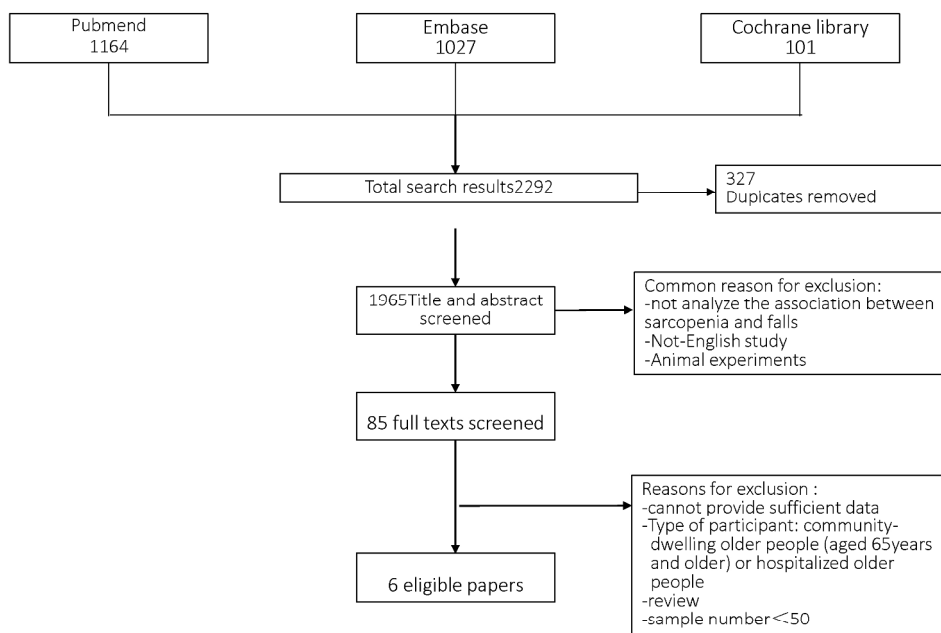
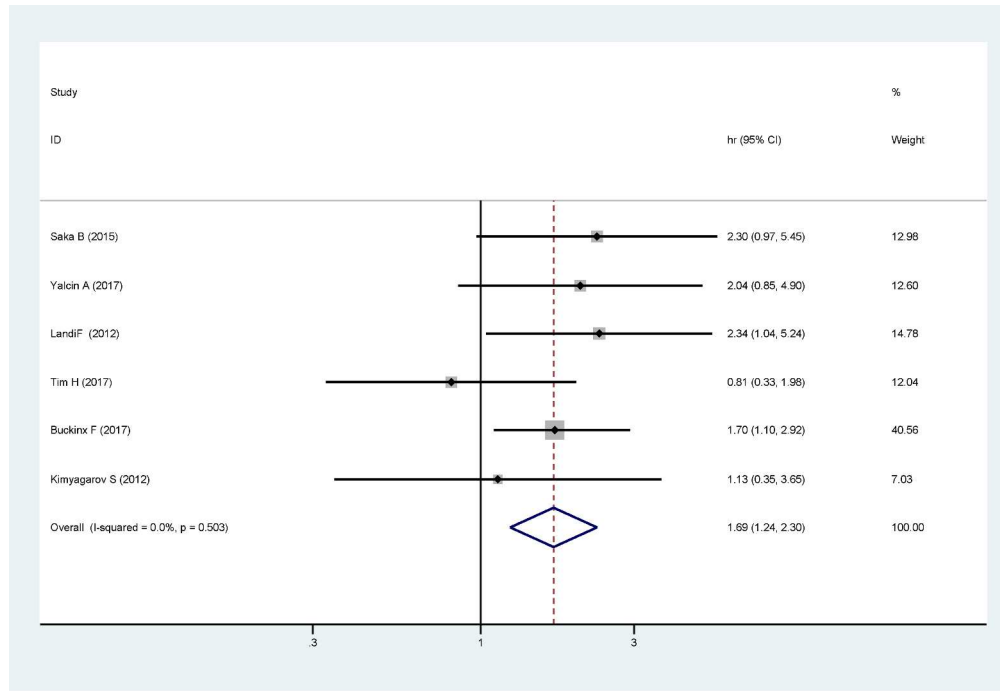


Figure 1. Search results and study selection

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Figure 2. Meta-analysis of the association between Sarcopenia and mortality among older nursing home residents

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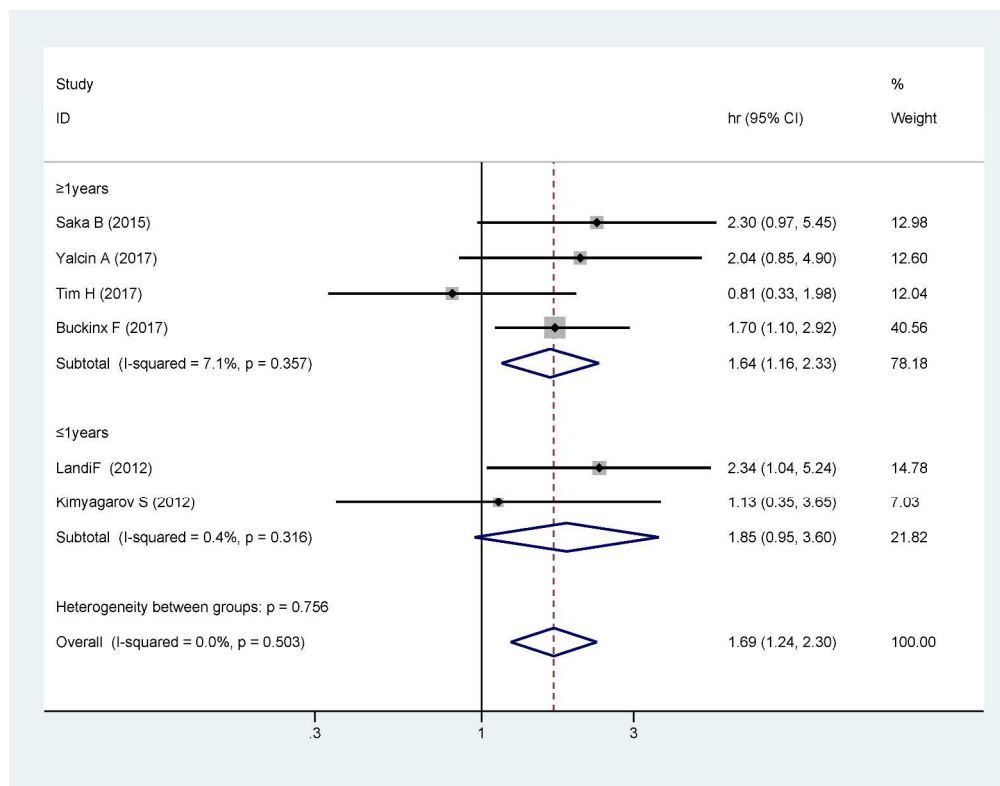


Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

277x215mm (300 x 300 DPI)

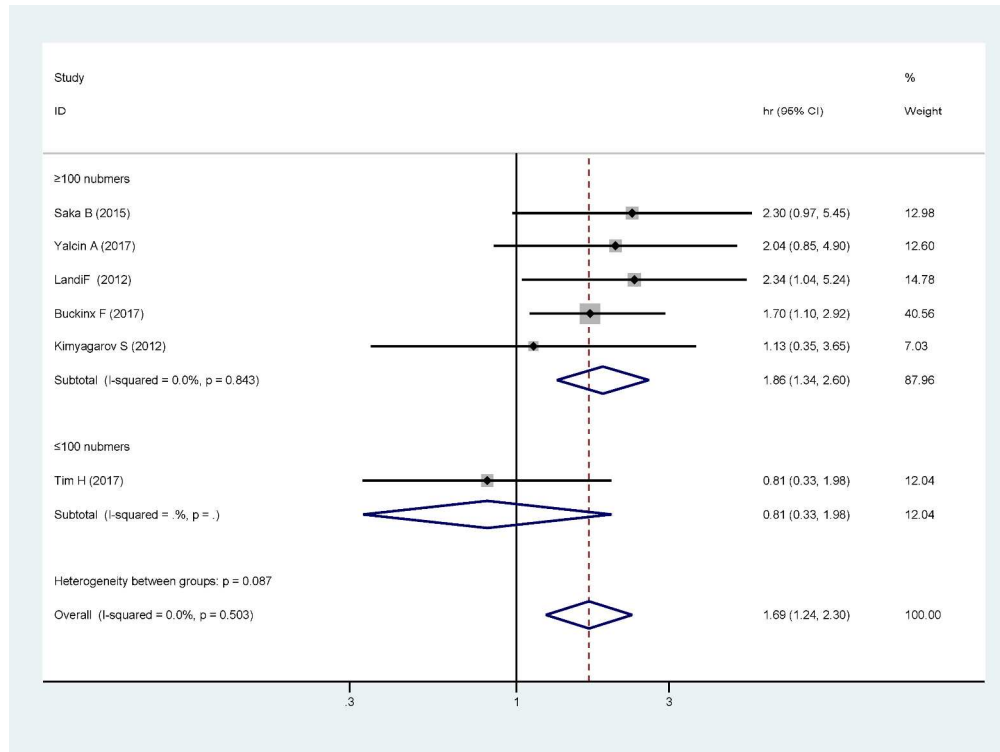


Figure 4. Subgroup analyses of the meta-analysis according to the sample size

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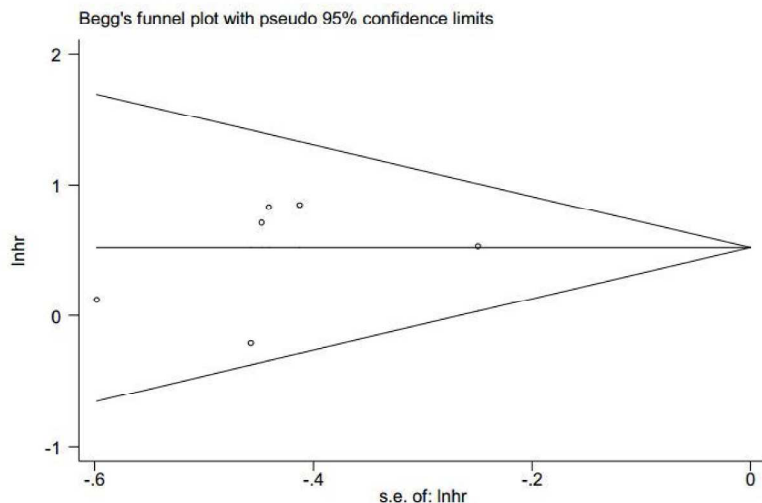


Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

318x206mm (300 x 300 DPI)

view only

BMJ Open

Sarcopenia as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis

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3 **Sarcopenia as a predictor of all-cause mortality among older nursing home**
4 **residents: a systematic review and meta-analysis**
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Abstract

Objectives: This study aims to review the evidence of sarcopenia as a predictor of all-cause mortality among nursing home residents.

Design: A systematic review and meta-analysis of cohort studies was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data sources: PubMed, EMBASE, and the Cochrane Library databases were searched for relevant articles.

Participants: Nursing home residents.

Primary and secondary outcome measures: All-cause mortality

Data analysis: Summary-adjusted hazard ratios (HRs) or risk ratios (RRs) were calculated by fixed-effects model. The risk of bias was assessed by Newcastle-Ottawa Scale.

Results: Of 2292 studies identified through the systematic review, six studies (1494 participants) were included in the meta-analysis. Sarcopenia was significantly associated with a higher risk for all-cause mortality among nursing home residents (pooled HR=1.86, 95% confidence interval [95% CI] =1.42-2.45, P=0.000, $I^2 =0$). In addition, the subgroup analysis for length of follow-up demonstrated that a follow-up period of 1 year or more of analysis was associated with all-cause mortality (pooled HR 1.87, [95%CI]=1.38- 2.52, p= p=0.00); however, this was not found with the follow-up period less than 1 year. Furthermore, sarcopenia was significantly associated with the risk of mortality among older nursing home residents when using bioelectrical impedance analysis to diagnosis muscle mass (pooled HR=1.88, 95% CI = 1.39- 2.53, p=0.00); whereas, it was not found with anthropometric measures to diagnosis muscle mass.

Conclusion: Sarcopenia is a significant predictor of all-cause mortality among older nursing home residents. Therefore, it is important to diagnose sarcopenia and to treat the condition to reduce mortality rates among nursing home residents.

PROSPEERO registration number: CRD42018081668

Key words: Sarcopenia; All-cause mortality; Nursing Home; Meta-analysis

Strengths and limitations of this study

1. We used an extensive search process in an electronic database and assessed methodologic quality and tested the heterogeneity and publication bias among the included studies.
2. This systematic review and meta-analysis assessed the overall quality of the evidence using a Newcastle Ottawa Scale (NOS) approach for prospective observational studies and conducted a meta-analysis and subgroup analysis.
3. The pooled results showed good consistency (low between-study heterogeneity) because we used the same unified diagnostic criteria of sarcopenia and the same population (nursing home residents).
4. The studies included in this analysis were insufficient, and the size sample was relatively small.
5. Different cutoff values for the muscle mass might affect the relationship between sarcopenia and all-cause mortality.

1. Introduction

Sarcopenia is a common syndrome characterised by a loss of muscle mass and strength with functional impairment and adverse health outcomes due to cumulative deficits of multiple systems¹. Nursing home residents are at a particularly high risk for sarcopenia². According to studies, the prevalence of sarcopenia was 1-29% for community-dwelling older adults, 14-85.4% in nursing homes²⁻⁴ and 10-24.3% for those in hospitals⁵. Sarcopenia leads to a worse outcome in elderly people, including physical disability, falls, fractures, poor quality of life, mortality and hospitalisation⁶⁻⁸. Among these, mortality might be considered the most important outcome in elderly people. So far, the relationship between mortality and operational criteria that define sarcopenia has been well described in community-dwelling older adults and hospitalised patients. A recent meta-analysis study, Liu⁹ *et al.*, analysed sarcopenia and mortality and concluded that sarcopenia is a predictor of all-cause mortality among community-dwelling older people. However, there is no consistent conclusion

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3 regarding the relationship between sarcopenia and mortality among nursing home
4 residents. It has been shown that the mortality rate in nursing homes¹⁰ is
5 approximately 2-fold higher than that in the community¹¹⁻¹³; therefore, it is very
6 important to confirm the risk factors for mortality among nursing home residents.
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10 Several studies found that elderly people with sarcopenia were predictors of
11 all-cause mortality among nursing home residents^{14, 15}. However, some studies did
12 not find any significant relationship between sarcopenia and all-cause mortality¹⁶⁻¹⁹.
13 Given the observed contradictory relationship between sarcopenia and all-cause
14 mortality among nursing home residents in some studies, further studies are needed.
15 However, no systematic reviews of meta-analysis studies on this topic have been
16 conducted in the literature. Therefore, our study aims to identify and compare
17 prospective cohort studies examining sarcopenia as a predictor of all-cause mortality
18 among nursing home residents according to the Preferred Reporting Items for
19 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
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29 **2. Materials and methods**

30 This meta-analysis was registered with the international prospective Register for
31 Systemic Reviews (CRD42018081668) and conducted according to the PRISMA
32 guidelines²⁰.
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36 **2.1. Search strategy and selection criteria**

37 A systematic literature search was conducted in MEDLINE (via PubMed 1946 to
38 November 2017), EMBASE (via EMBASE November 2017) and Cochrane CENTRAL
39 Library (via Cochrane Library November 2017). The search strategy was tailored
40 according to each database. We used a combination of key words such as mortality
41 (mortality*), OR death (death*), OR survival (survival*) and sarcopenia (sarcopenia*),
42 as well as MeSH terms. We also used subject terms and truncation symbols in our
43 search strategy. We searched the potential grey studies through Google Scholar.
44 Furthermore, we carried out a manual search on the references of included studies.
45 The full search strategy for three databases has been provided as a supplementary
46 file.
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56 **2.2. Study selection**

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3 These studies identified by our search strategy were reviewed by teams of two
4 independently blinded reviewers (Zhang XM and Wang CH) who evaluated each title
5 and abstract. In case of disagreement whether to include or exclude studies, the
6 issue was discussed and a third reviewer evaluated the study until the reviewers
7 reached consensus.
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10 11 12 **2.3. Inclusion and exclusion criteria**

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14 The following eligibility and exclusion criteria were prespecified. Studies had to
15 fulfil the following four inclusion criteria: (1) prospective cohort studies, (2) studies
16 investigating whether sarcopenia was a predictor of mortality, (3) studies reporting
17 clear diagnostic criteria for sarcopenia, (4) type of participant: elderly adult in nursing
18 home or nursing care. Exclusion criteria were as follows: (1) Type of participant:
19 community-dwelling older people (aged 65 years or older) or hospitalised older
20 people; (2) article type: only abstract, letters and laboratory research; review articles;
21 (3) insufficient data; (4) other languages of studies, except English; (5) no clear
22 definition of sarcopenia.
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30 31 **2.4. Data extraction**

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33 Two investigators (Zhang XM, Wang CH) independently abstracted the data from
34 the selected studies using a standardised data-abstraction form. The following
35 information was extracted from included papers: author, country, year of publication,
36 demographic characteristics of participants (e.g., sample size, male proportion),
37 measurement methods of sarcopenia, follow-up period, Adjusted variable, and study
38 quality. The reviewers cross-checked all extracted data. Disagreements were resolved
39 by discussion until consensus was reached.
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45 46 **2.5. Patient and Public Involvement**

47 Our meta-analysis was based on secondary data; therefore, the ethical approval,
48 patient consent or Public Involvement was not necessary.
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50 51 **2.6. Assessment of risk bias**

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53 Assessment of risk of bias was performed by two independent reviewers (Zhang
54 XM, Wang CH) according to the Newcastle Ottawa Scale (NOS)²¹: (1)
55 representativeness of the exposed cohort, (2) comparability of group, (3) blinding of
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3 investigators who measured outcomes, (4) the time and completeness of follow-up,
4 (5) contamination bias, and (6) other potential sources of bias. The total score of the
5 scale is 9 points. When the total score is ≥ 5 points, it is considered a high-quality
6 research.
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10 **2.7. Statistical analysis**

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12 The STATA version 14.0 (Stata Corp., College Station, TX, USA) was
13 independently used for all analyses by two authors (Zhang XM, Dou QL). Hazard
14 ratios (HRs), odds ratio (ORs) and their 95% CIs of mortality for sarcopenia compared
15 with nonsarcopenia were extracted from studies for future meta-analysis. RR was
16 considered equivalent to HR in our prospective cohort studies, which was reported in
17 Carole Willi's²² study and Ahmed N Mahmoud's study²³. If a study reported the effect
18 size as an OR, it was converted to RR using a previously described formula²⁴.
19 Subgroup analyses were conducted by different diagnosis tools for muscle mass and
20 follow-up period if there was more than one study in the subgroup. The statistical
21 heterogeneity among the included studies was examined with Cochran's Q statistic
22 using chi-square and I^2 statistics, and I^2 value of 25%, 50% and 75% represented the
23 cutoff of low, moderate and high heterogeneity, respectively. If heterogeneity was
24 found to be reasonably high between studies, the random-effects model was used.
25 Otherwise, the fixed-effects model was used. Results were illustrated using forest
26 plots, and Begg's Test was done to plot the logHR against its standard error for
27 assessment of potential publication bias.
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42 **3. Results**

43 **3.1. Search results**

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45 The literature search strategy initially identified 2292 articles. After removal of
46 duplicates, 1965 articles were screened for potential eligibility. A total of 85
47 publications remained for further consideration. Then we screened titles and
48 abstracts and removed unrelated articles. Of these articles, 30 were removed
49 because of not cohort studies (e.g., review articles, conference documents,
50 cross-sectional study, case-control study), and six were removed because they had no
51 clear definition of sarcopenia; moreover, 41 were removed on account of different
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3 study population: community-dwelling older people, patients in hospital, and used
4 the same cohorts (n = 2). These studies were screened according to the predefined
5 inclusion and exclusion criteria for inclusion in the meta-analysis, resulting in a total
6 of six eligible studies (Figure 1).
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10 **3.2 Included studies**

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12 Six prospective cohort studies were included in our meta-analysis with 1494
13 total participants. Study characteristics of included papers are displayed in table 1.
14 Two studies were conducted in Turkey^{25, 26}, one study in Italy²⁷⁻²⁹, one study in
15 Australia³⁰, one study in Belgium and one study in Israel. All the studies selected
16 all-cause mortality as the clinical outcome and used the sarcopenia criteria of the
17 European Working Group for Sarcopenia (EWGSOP). The EWGSOP¹ recommends
18 using the presence of both low muscle function (strength or performance) and low
19 muscle mass for the diagnosis of sarcopenia. Thus, diagnosis of sarcopenia in the
20 present study required the documentation of low muscle mass plus the
21 documentation of either low muscle strength or low physical performance. The
22 prevalence of sarcopenia ranged from 32.8 to 73.3%. The largest study consisted of
23 662 men and women, and the smallest cohort had only 58 individuals. Follow-up
24 periods were not longer varying from 6 months to 24 months, and the adjusted HR
25 was displayed in four studies, and one used OR and the other used RR. Table 2 shows
26 the different tools and cutoff of muscle mass, muscle strength and physical
27 performance. Four studies used bioelectrical impedance analysis (BAI) as a diagnostic
28 criterion for muscle mass, and the other two studies used anthropometric measures
29 as diagnostic criteria.
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45 **3.3 Quality assessment**

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47 The methodologic quality evaluation using NOS of all items is shown in Table 3.
48 The score of each study ranged from six to nine. The scores of five studies were more
49 than seven.
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52 **3.4 Sarcopenia as a predictor of mortality**

53 **3.4.1 Meta-analysis of studies**

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55 Six studies examined the association between sarcopenia and mortality among
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3 nursing home residents. The pooled HRs values were calculated by fixed-effects
4 models. As show in Figure 2, the HRs of all-cause mortality for sarcopenia versus
5 nonsarcopenia was 1.86 (95%CI=1.42-2.45, P=0.001). No significant heterogeneity
6 was observed across these studies (Q-value=4.82, degree of freedom=5, I²=0%,
7 p=0.438).
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10 11 12 3.4.2 Subgroup analysis 13

14 The six studies with HR of all-cause mortality risks for sarcopenia among nursing
15 home residents were further analysed by subgroup. Figure 3 compares all-cause
16 mortality risk stratified by length of follow-up for sarcopeina. Two studies with a
17 follow-up period less than 1 year for sarcopenia (pooled HR 1.85, 95%CI 0.95–3.60,
18 p=0.070); whereas the analysis of other four studies had a follow-up period of 1 year
19 or more (pooled HR 1.87,95%CI 1.38-2.52, p=0.00). Figure 4 shows sarcopenia was
20 significantly associated with the risk of morbidity among nursing home residents
21 when using BIA to diagnose muscle mass (pooled effect size=1.88,95% CI =1.39-
22 2.53,p=0.00), whereas it was not associated when using anthropometric measures to
23 diagnosis muscle mass (pooled effect size=1.79,95% CI=0.89-3.59,p=0.10).
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32 3.4.3 Publication bias assessment 33

34 There was no significant publication bias among the studies using Begg's test:
35 P=0.386 (Figure 5).
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40 4. Discussion

41 In this meta-analysis, we found evidence suggesting the risk of all-cause
42 mortality among nursing home residents with sarcopenia was higher than that
43 among nursing home residents without sarcopenia. To the best of our knowledge,
44 this is the first meta-analysis to explore the relationship between sarcopenia and
45 all-cause mortality among nursing home residents. Our study indicated assessing
46 sarcopenia is really important among the elderly that live in nursing homes.
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52 Ping Liu⁹ *et al.* implemented a systematic review and meta-analysis regarding
53 the association of sarcopenia with mortality in 2016, published in 2017. However,
54 this review included a population entirely of community-dwelling older people. So far,
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3 Shu-Fang Chang³¹ and Beaudart³² both performed a systematic review to evaluate
4 the link between sarcopenia and all-cause mortality; however, there were some
5 methodologic shortcomings, such as various diagnostic criteria of sarcopenia, crude
6 ORs as effect, various population involving community-dwelling older people and
7 hospitalised patients. Although a subgroup of nursing home residents was analysed
8 in Beaudart's study, there is only two studies that was assessed, which maybe
9 underestimated or overestimated their result. Our review included six studies which
10 focus only on the association of mortality and sarcopenia in nursing home residents.
11 We adopted the same diagnostic criteria of sarcopenia (EWGSOP) and the same type
12 of population (nursing home residents) to decrease clinical heterogeneity.
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21 This meta-analysis of six cohort studies shows sarcopenia is an important
22 predictor of all-cause mortality among nursing home residents. The pooled HR value
23 of all-cause mortality was 1.86 (95%CI=1.41-2.45, P=0.000, I² = 0%). The perfect I²
24 suggesting no significant heterogeneity was shown across these research. In addition,
25 our study's pooled HR value is higher than that of Ping Liu (1.60 95%CI: 1.24–2.06);
26 the primary reason was the different type of population. Those living in a nursing
27 home usually had worse health conditions and more comorbidities, more disability
28 and more geriatric syndromes, such as cognitive dysfunction and malnutrition^{17, 33-35}.
29 This comprehensive risk factor may aggravate the process of sarcopenia.
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38 The prevalence of sarcopenia was 32.8-73.3%, which is higher than that in other
39 studies. The difference was mainly due to the mean age, various population and
40 different diagnostic tools, particularly the ways researchers measured muscle mass.
41 Sarcopenia was associated with all-cause mortality when using BIA to diagnose
42 muscle mass; whereas it was not associated when using anthropometric measures to
43 diagnose muscle mass. According to the EWGSOP¹, BIA is the most common tool for
44 diagnosing muscle mass; moreover, the test is inexpensive, easy to use, readily
45 reproducible and appropriate for both ambulatory and bedridden patients, which
46 may be considered a portable alternative toDXA (Dual Energy X-ray Absorptiometry)
47 in nursing homes. However, the method of anthropometric measures was based on
48 mid-upper-arm circumference and skin fold thickness³⁶; therefore, age-related
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3 changes in fat deposits and loss of skin elasticity contribute to errors of estimation in
4 older nursing home residents, which are prone to produce errors³⁷. Furthermore,
5 anthropometric measures were not recommended for routine use in the diagnosis of
6 sarcopenia. The subgroup of length of follow-up analysis demonstrated that
7 follow-up period of 1 year or more of analysis was associated with all-cause mortality
8 (pooled HR=1.87,95%CI 1.38-2.52, p=0.000); however, this was not found with the
9 follow-up period of less than 1 year. The reason may be, with the time of aging,
10 sarcopenia will aggravatingly impact patient survival, which may increase the
11 mortality rates.
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20 The underlying mechanisms between sarcopenia and a higher risk of all-cause
21 mortality did not have a conclusion; some aspects should be mentioned at least.
22 Firstly, the association between sarcopenia and mortality may be explained by the
23 hypothesised adverse effects of a low muscle mass in older people. Several studies
24 showed that low muscle mass is highly associated with increased mortality³⁸⁻⁴⁰. In
25 addition, elderly people in nursing homes are at high risk of malnutrition⁴¹, which
26 aggravates low muscle mass, resulting in an increased mortality rate. Secondly,
27 sarcopenia is linked to multiple factors ranging from aging process⁴², multiple chronic
28 health conditions, unhealthy lifestyle⁴³, hormonal factors⁴⁴, inflammation⁴⁵ and so
29 on⁴⁶. Meanwhile, the above factors are consider linked to mortality and the
30 development of multifactor worsened the situation of sarcopenia, leading to a
31 passive adaption to adversity or external stressors, which in turn generate increased
32 poor adverse outcomes⁴⁷. Thirdly, according to the study of Fried⁴⁸ *et al.*, sarcopenia
33 played a critical etiologic role in the frailty process, which is related, through frailty,
34 to pernicious consequences—for instance, recurrent falls, bone fracture, disability,
35 multiple emergency room visits and hospital admissions and eventually death^{49, 50}.
36 Moreover, sarcopenia is considered to increase the risk of falls among the elderly⁵¹,
37 and falls were the major causes of death in nursing home residents⁵². Sarcopenia is a
38 geriatric syndrome rather than a disease; the mechanism of sarcopenia must be
39 complex, which needs more research to explore.
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56 Our meta-analysis review has multiple strengths and some limitations. One

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3 strength is we used an extensive search process in electronic databases and assessed
4 methodologic quality and tested the heterogeneity and publication bias among the
5 included studies. Another strength was using the same unified diagnostic criteria of
6 sarcopenia (EWGSOP) and the same population (nursing home residents) to reduce
7 heterogeneity and improve the research quality. Our study had some limitations.
8 Firstly, few included studies did not present the same confounding factors that were
9 incorporated into the meta-analyses, which underestimated or overestimated our
10 results. Especially, the Mini-Nutritional Assessment that was not included in two
11 studies. However, malnutrition is very high among nursing home residents⁴¹. A study
12 has shown that malnutrition is a risk for mortality among nursing home residents¹⁷.
13 Another concern was that the cutoff for the muscle mass was different in some
14 studies, which will cause the prevalence of Sarcopenia to be various, thus potentially
15 influencing the result. The studies included in this analysis were insufficient, and the
16 sample size was relatively small. Thirdly, the language of studies was limited to
17 English, and consequently we may have missing data from important studies
18 published in other languages, which may result in potential language bias. In addition,
19 the follow-up was relatively short for the necessary latency, which may
20 underestimate the results.
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36 **5. Conclusion**

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38 This study provides evidence that sarcopenia is a significant predictor of
39 all-cause mortality among nursing home residents based on the comprehensive
40 systematic review and meta-analysis. Further studies are needed to provide evidence
41 for specific interventions to prevent and treat sarcopenia, which can reduce mortality
42 in people living in a nursing home.
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47 **6. Acknowledgements**

48
49 The authors thank the staffs of the Department of Emergency Medicine,
50 people's hospital of Baoan ShenZhen for their guidance and support.
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53 **7. Financial Support**

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2
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4 not-for-profit sectors. No sponsors had any role in the design, methods, subject
5 recruitment, data collections, analysis or preparation of this manuscript.
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8 **8. Contributors**

9
10 Xiaoming Zhang was responsible for producing the initial draft of the manuscript.

11
12 Conghua Wang was responsible for data extraction and for producing the initial draft
13 of the manuscript.
14

15
16 Qingli Dou was responsible for data extraction.

17
18 Wenwu Zhang was responsible for screening the papers and quality assessment.

19
20 Xiaohua Xiewas responsible for screening the papers.

21
22 Yunzhi Yang was responsible for quality assessment, statistical analysis and revision
23 of the manuscript.
24

25 All the authors approved the final version of the manuscript
26

27 **9. Conflict of Interest**

28
29 None of the authors have any conflict of interest to declare.
30

31 **10. Data Sharing Statements**

32 All the data can be found in the electronic databases (PubMed, EMBASE, and
33 the Cochrane Library).
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Table 1 Summary of Included Studies on Sarcopenia Associated with All-cause Mortality

Author	Country	Year	Male	Sample number	Age of patients, years	Sarcopenia Criteria	Prevalence%	Follow-up period	Outcome	Effect Measure	Adjusted or Crude HR/OR	Quality*
Saka B	Turkey	2015	51%	402	78.0±7.9	EWGSOP	73.3	12 months	All-cause mortality	HR	Adjusted	8
Yalcin A	Turkey	2017	54.3%	141	79.17±7.99	EWGSOP	53.9	24 months	All-cause mortality	HR	1-3,6,12,14,29-34	7
Landi F	Italy	2012	25%	122	84.1±4.8	EWGSOP	32.8	6 months	All-cause mortality	HRs	1,2,29,30-32	8
Henwood T	Australia	2017	29.3%	58	85.7±8.2	EWGSOP	51.7	18 months	All-cause mortality	RR	1-3,14,28	6
Buckinx F	Belgium	2017	27.5%	662	83.2±8.99	EWGSOP	36.2	12 months	All-cause mortality	OR	1-27	7
Kimyagarov S	Israel	2012	41.2%	109	84.9±7.4	EWGSO	40.3	12 months	All-cause mortality	HR	1-3,35	7

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EWGSOP(European Working Group for Sarcopenia in Older Persons) defines sarcopenia in men as ALM adjusted for height squared <7.25 kg/m² combined with low hand-grip strength (<30 kg) and/or low gait speed(<0.8 m/s).

Quality* of the studies were assessed with Newcastle-Ottawa Scale(NOS);
(1)Age; (2)sex; (3) BMI; (4) Frailty; (5) Waist circumference;(6) Calf circumference; (7) Arm circumference; (8) Wrist circumference;(9)Walking support; (10) Drugs consumed; (11) Medical history; (12); MMSE: Mini-Mental State Examination; (13) Minnesota (14) MNA, Mini-Nutritional Assessment;(15) Body fat; (16) SF-36; (17) EuroQol five dimensions; (18) EuroQol-Visual Analogue Scale; (19); Katz score;(20) Fear of falling; (21) Tinetti test; (22) TUG test; (23) SPPB test; (24) Gait speed; (25) Grip strength; (26) Peak expiratory flow; (27) Isometric strength; (28) physical activity; (29) cerebrovascular diseases; (30) osteoarthritis; (31) chronic obstructive pulmonary disease; (32)activity of daily living impairment; (33)Diabetes; (34) Dementia; (35) Charlson comorbidity index

Table2 Study and Sarcopenia criteria

study	Sarcopenia criteria	Item,tool, Cutoff points	Muscle mass	Muscle strength	Physical performance	Ref		
		Tool	Cutoff points	Tool	Cutoff points	Tool	Cutoff point	
Yalcin A 2017	EWFSOP	BIA	Men:SMI ≤8.87Kg/m ² Women:SMI ≤6.42Kg/m ²	handgrip strength	Men:HGS<30Kg Women:HGS<20Kg	Gait speed: 4-m	≤ 0.8 m/s	18
Buckinx F 2017	EWFSOP	BIA	Men:SMI ≤8.87Kg/m ² Women:SMI ≤6.42Kg/m ²	Handgrip strength	None	SPPB: Short Physical Performance Battery	SPPB≤8	14
Henwood T	EWFSOP	BIA	Men:SMI <8.87 kg/m ² Women:SMI <6.42 kg/m ²	hand grip Strength	Men:HGS<30Kg Women:HGS<20Kg	SPPB: Short Physical Performance Battery	≤ 0.8 m/s	16

Saka B	EWFSOP	anthropometric measures	CC<31cm in men and women MuAMC < 23.8cm in men MUAMC < 23.3cm in women	hand grip Strength	Men:HGS<30Kg Women:HGS<20Kg	Gait speed: 4-m	≤ 0.8 m/s	17
Kimyagarov S	EWFSOP	anthropometric measures	Men:SMI <8.50 kg/m ² Women:SMI <5.75 kg/m ²	manual muscle testing	None	None	None	19
Landi F	EWFSOP	BIA	Men:SMI <8.87 kg/m ² Women:SMI <6.42 kg/m ²	hand grip Strength	Men:HGS<30Kg Women:HGS<20Kg	Gait speed: 4-m	≤ 0.8 m/s	15

Table 3
Result of the Newcastle-Ottawa scale quality assessment

Newcastle-Ottawa scale		Saka B 2015	Yalcin A 2017	Landi F 2012	Kimyagarov S 2012	Henwood T 2017	Buckinx F 2017
Selection(4)	Representativeness of the exposed cohort	1	1	1	1	1	1
	Selection of the non-exposed cohort	1	1	1	1	1	1
	Ascertainment of exposure	1	1	1	1	1	1
	Demonstration that outcome of interest was not present at start of	1	1	1	1	1	1

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	study						
Comparability(2)	Comparability of cohorts on the basis of the design or analysis	2	1	2	1	1	2
Outcome(3)	Assessment of outcome	1	1	1	1	1	1
	Was follow-up long enough for outcome to occur	0	0	0	0	0	0
	Adequacy of follow up of cohorts	1	1	1	1	1	1
Quality(9)	Total	8	7	8	7	6	7

For peer review only

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3 Figure 1. The flow diagram of studies selection.

4 Figure 2. Meta-analysis of the association between sarcopenia and mortality among older
5 nursing home residents.

6 Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up.

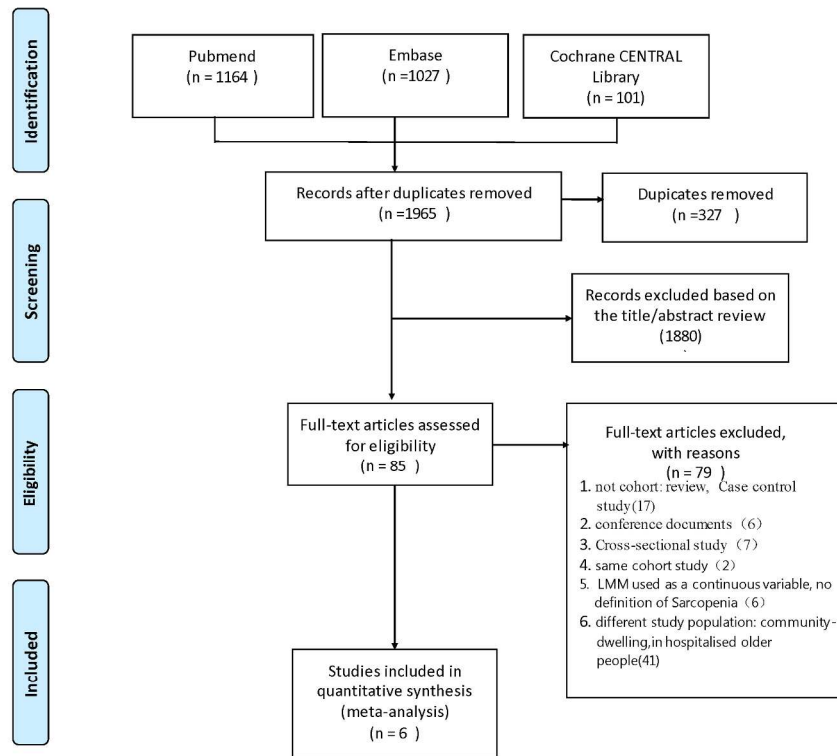
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8 Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle
9 mass.

10 Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents.
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Figure 1. The flow diagram of studies selection.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1. The flow diagram of studies selection.

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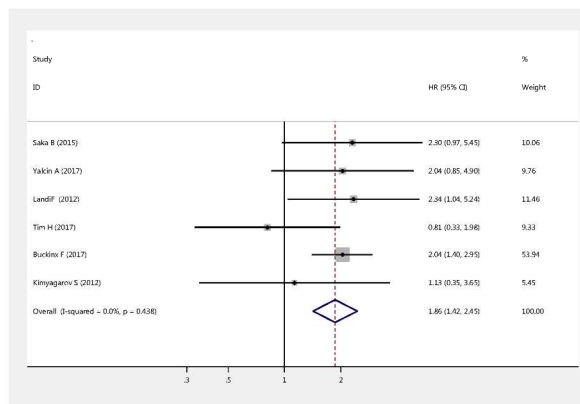


Figure 2. Meta-analysis of the association between sarcopenia and mortality among older nursing home residents.

Figure 2. Meta-analysis of the association between sarcopenia and mortality among older nursing home residents.

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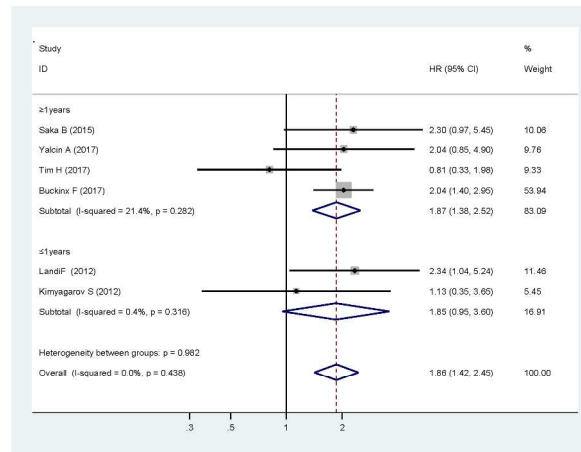


Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

Subgroup analyses of the meta-analysis according to length of follow-up.

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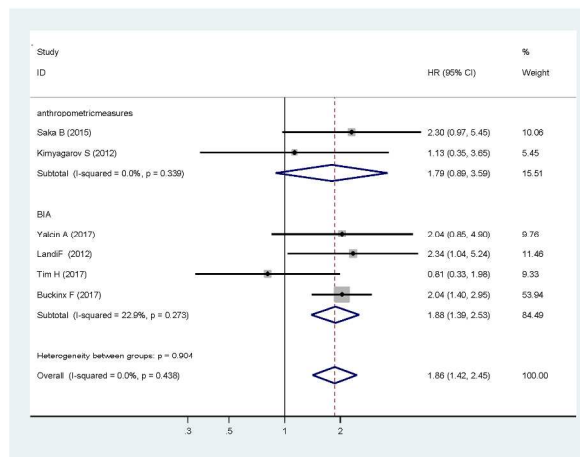


Figure 4: Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

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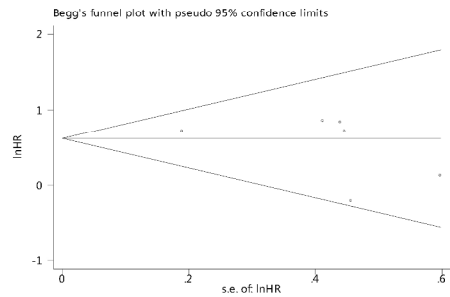


Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

Funnel plot of sarcopenia and all-cause mortality among older nursing home residents.

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MEDLINE (via PubMed)

- #1: Search sarcopenia*
- #2: Search "Sarcopenia"[Mesh]
- #3: Search ("Sarcopenia"[Mesh]) OR sarcopenia*
- #4: Search "Mortality"[Mesh]
- #5: Search mortality*
- #6: Search "Death"[Mesh]
- #7: Search death*
- #8: Search survival*
- #9: Search "Survival"[Mesh]
- #10: Search (((("Survival"[Mesh]) OR survival*) OR death*) OR "Death"[Mesh]) OR mortality*) OR "Mortality"[Mesh]
- #11: Search ((((((("Survival"[Mesh]) OR survival*) OR death*) OR "Death"[Mesh]) OR mortality*) OR "Mortality"[Mesh])) AND (("Sarcopenia"[Mesh]) OR sarcopenia*)

Cochrane CENTRAL Library

- #1: Search sarcopenia*
- #2: Search MeSH descriptor: [Sarcopenia] explode all trees
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- #5: Search mortality*
- #6: Search MeSH descriptor: [death] explode all trees
- #7: Search death*
- #8: Search survival*
- #9: Search MeSH descriptor: [survival] explode all trees
- #10: #4 OR #5 OR #6 OR #7 OR #8 OR #9
- #11: # 3 AND #10

EMBASE

- #1: 'sarcopenia'/exp
- #2: 'mortality'/exp
- #3: 'death'/exp
- #4: 'survival'/exp
- #5: #2 OR #3 OR #4
- #6: #1 AND #5



PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



PRISMA 2009 Checklist

Page 1 of 2

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

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Sarcopenia as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis

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3 **Sarcopenia as a predictor of all-cause mortality among older nursing home**
4 **residents: a systematic review and meta-analysis**
5

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Abstract

Objectives: This study aims to review the evidence of sarcopenia as a predictor of all-cause mortality among nursing home residents.

Design: systematic review and meta-analysis of observational cohort studies

Data sources: PubMed, EMBASE, and the Cochrane Library databases were searched for relevant articles.

Participants: Nursing home residents.

Primary and secondary outcome measures: All-cause mortality

Data analysis: Summary-adjusted hazard ratios (HRs) or risk ratios (RRs) were calculated by fixed-effects model. The risk of bias was assessed by Newcastle-Ottawa Scale.

Results: Of 2292 studies identified through the systematic review, six studies (1494 participants) were included in the meta-analysis. Sarcopenia was significantly associated with a higher risk for all-cause mortality among nursing home residents (pooled HR=1.86, 95% confidence interval [95% CI] =1.42-2.45, P=0.000, I² =0). In addition, the subgroup analysis for length of follow-up demonstrated that a follow-up period of 1 year or more of analysis was associated with all-cause mortality (pooled HR 1.87, [95%CI]=1.38- 2.52, p= p=0.000); however, this was not found with the follow-up period less than 1 year. Furthermore, sarcopenia was significantly associated with the risk of mortality among older nursing home residents when using bioelectrical impedance analysis to diagnosis muscle mass (pooled HR=1.88, 95% CI = 1.39- 2.53, p=0.000); whereas, it was not found with anthropometric measures to diagnosis muscle mass.

Conclusion: Sarcopenia is a significant predictor of all-cause mortality among older nursing home residents. Therefore, it is important to diagnose sarcopenia and to treat the condition to reduce mortality rates among nursing home residents.

PROSPEERO registration number: CRD42018081668

Key words: Sarcopenia; All-cause mortality; Nursing Home; Meta-analysis

Strengths and limitations of this study

1. To the best of our knowledge, this is the first meta-analysis to explore the relationship between sarcopenia and all-cause mortality among elderly nursing home residents.
2. An extensive search process in an electronic database was used and methodologic quality was assessed; we also tested the heterogeneity and publication bias and performed sensitivity analysis among the included studies.
3. This systematic review and meta-analysis assessed the overall quality of the evidence using a Newcastle Ottawa Scale (NOS) approach for prospective observational studies and conducted a meta-analysis and subgroup analysis.
4. The number of studies included in this analysis were insufficient, and the size sample was relatively small.
5. Different cutoff values for the muscle mass might affect the relationship between sarcopenia and all-cause mortality.

1. Introduction

Sarcopenia is a common syndrome characterised by a loss of muscle mass and strength with functional impairment and adverse health outcomes due to cumulative deficits of multiple systems¹. Nursing home residents are at a particularly high risk for sarcopenia². According to studies, the prevalence of sarcopenia was 1-29% for community-dwelling older adults, 14–85.4% in nursing homes²⁻⁴ and 10-24.3% for those in hospitals⁵. Sarcopenia leads to a worse outcome in elderly people, including physical disability, falls, fractures, poor quality of life, mortality and hospitalisation⁶⁻⁸. Among these, mortality might be considered the most important outcome in elderly people. So far, the relationship between mortality and operational criteria that define sarcopenia has been well described in community-dwelling older adults and hospitalised patients. A recent meta-analysis study, Liu⁹ *et al.*, analysed sarcopenia and mortality and concluded that sarcopenia is a predictor of all-cause mortality among

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3 community-dwelling older people. However, there is no consistent conclusion
4 regarding the relationship between sarcopenia and mortality among nursing home
5 residents. It has been shown that the mortality rate in nursing homes¹⁰ is approximately
6 2-fold higher than that in the community¹¹⁻¹³; therefore, it is very important to confirm
7 the risk factors for mortality among nursing home residents.
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12 Several studies found that elderly people with sarcopenia were predictors of
13 all-cause mortality among nursing home residents^{14, 15}. However, some studies did not
14 find any significant relationship between sarcopenia and all-cause mortality¹⁶⁻¹⁹. Given
15 the observed contradictory relationship between sarcopenia and all-cause mortality
16 among nursing home residents in some studies, further studies are needed. However, no
17 systematic reviews of meta-analysis studies on this topic have been conducted in the
18 literature. Therefore, our study aims to identify and compare prospective cohort studies
19 examining sarcopenia as a predictor of all-cause mortality among nursing home
20 residents according to the Preferred Reporting Items for Systematic Reviews and
21 Meta-Analyses (PRISMA) guidelines.
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30 **2. Materials and methods**

31 This meta-analysis was registered with the international prospective Register for
32 Systemic Reviews (CRD42018081668) and conducted according to the PRISMA
33 guidelines²⁰.
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38 **2.1. Search strategy and selection criteria**

39 A systematic literature search was conducted in MEDLINE (via PubMed 1946 to
40 November 2017), EMBASE (via EMBASE November 2017) and Cochrane
41 CENTRAL Library (via Cochrane Library November 2017). The search strategy was
42 tailored according to each database. We used a combination of key words such as
43 mortality (mortality*), OR death (death*), OR survival (survival*) and sarcopenia
44 (sarcopenia*), as well as MeSH terms. We also used subject terms and truncation
45 symbols in our search strategy. We searched the potential grey studies through Google
46 Scholar. Furthermore, we carried out a manual search on the references of included
47 studies. The full search strategy for three databases has been provided as a
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3 supplementary file.

4 5 **2.2. Study selection**

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7 These studies identified by our search strategy were reviewed by teams of two
8 independently blinded reviewers (Zhang XM and Wang CH) who evaluated each title
9 and abstract. In case of disagreement whether to include or exclude studies, the issue
10 was discussed and a third reviewer evaluated the study until the reviewers reached
11 consensus.
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16 **2.3. Inclusion and exclusion criteria**

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18 The following eligibility and exclusion criteria were prespecified. Studies had to
19 fulfil the following four inclusion criteria: (1) prospective cohort studies, (2) studies
20 investigating whether sarcopenia was a predictor of mortality, (3) studies reporting
21 clear diagnostic criteria for sarcopenia, (4) type of participant: elderly adult in nursing
22 home or nursing care. Exclusion criteria were as follows: (1) Type of participant:
23 community-dwelling older people (aged 65 years or older) or hospitalised older people;
24 (2) article type: only abstract, letters and laboratory research; review articles; (3)
25 insufficient data; (4) other languages of studies, except English; (5) no clear definition
26 of sarcopenia.
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34 **2.4. Data extraction**

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36 Two investigators (Zhang XM, Wang CH) independently abstracted the data from
37 the selected studies using a standardised data-abstraction form. The following
38 information was extracted from included papers: author, country, year of publication,
39 demographic characteristics of participants (e.g., sample size, male proportion),
40 measurement methods of sarcopenia, follow-up period, Adjusted variable, and study
41 quality. The reviewers cross-checked all extracted data. Disagreements were resolved
42 by discussion until consensus was reached.
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49 **2.5. Assessment of risk bias**

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51 Assessment of risk of bias was performed by two independent reviewers (Zhang
52 XM, Wang CH) according to the Newcastle Ottawa Scale (NOS)²¹: (1)
53 representativeness of the exposed cohort, (2) comparability of group, (3) blinding of
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3 investigators who measured outcomes, (4) the time and completeness of follow-up, (5)
4 contamination bias, and (6) other potential sources of bias. The total score of the scale is
5 9 points. When the total score is ≥ 5 points, it is considered a high-quality research.
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8 **2.6. Statistical analysis**

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10 The STATA version 14.0 (Stata Corp., College Station, TX, USA) was
11 independently used for all analyses by two authors (Zhang XM, Dou QL). Hazard ratios
12 (HRs), odds ratio (ORs) and their 95% CIs of mortality for sarcopenia compared with
13 nonsarcopenia were extracted from studies for future meta-analysis. RR was
14 considered equivalent to HR in our prospective cohort studies, which was reported in
15 Carole Willi's²² study and Ahmed N Mahmoud's study²³. If a study reported the effect
16 size as an OR, it was converted to RR using a previously described formula²⁴. All the
17 effect of HR or RR was converted to $\ln(\text{HR})$ or $\ln(\text{RR})$ for ratio in meta-analysis,
18 Subgroup analyses were conducted by different diagnosis tools for muscle mass and
19 follow-up period if there was more than one study in the subgroup. The statistical
20 heterogeneity among the included studies was examined with Cochran's Q statistic
21 using chi-square and I^2 statistics, and I^2 value of 25%, 50% and 75% represented the
22 cut-off of low, moderate and high heterogeneity, respectively. If heterogeneity was
23 found to be reasonably high between studies, the random-effects model was used.
24 Otherwise, the fixed-effects model was used. Results were illustrated using forest plots,
25 and Begg's Test was done to plot the log HR against its standard error for assessment of
26 potential publication bias.
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41 **2.7. Patient and Public Involvement**

42 The patients or public were not involved in the study.
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44 **3. Results**

45 **3.1. Search results**

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47 The literature search strategy initially identified 2292 articles. After removal of
48 duplicates, 1965 articles were screened for potential eligibility. A total of 85
49 publications remained for further consideration. Then we screened titles and abstracts
50 and removed unrelated articles. Of these articles, 30 were removed because of non-
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3 cohort studies (e.g., review articles, conference documents, cross-sectional study,
4 case-control study), and six were removed because they had no clear definition of
5 sarcopenia; moreover, 41 were removed on account of different study population:
6 community-dwelling older people, patients in hospital, and used the same cohorts (n =
7 2). These studies were screened according to the predefined inclusion and exclusion
8 criteria for inclusion in the meta-analysis, resulting in a total of six eligible studies
9 (Figure 1).

16 **3.2 Included studies**

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18 Six prospective cohort studies were included in our meta-analysis with 1494 total
19 participants. Study characteristics of included papers are displayed in table 1. Two
20 studies were conducted in Turkey^{25, 26}, one study in Italy²⁷⁻²⁹, one study in Australia³⁰,
21 one study in Belgium and one study in Israel. All the studies selected all-cause
22 mortality as the clinical outcome and used the sarcopenia criteria of the European
23 Working Group for Sarcopenia (EWGSOP). The EWGSOP¹ recommends using the
24 presence of both low muscle function (strength or performance) and low muscle mass
25 for the diagnosis of sarcopenia. Thus, diagnosis of sarcopenia in the present study
26 required the documentation of low muscle mass plus the documentation of either low
27 muscle strength or low physical performance. The prevalence of sarcopenia ranged
28 from 32.8 to 73.3%. The largest study consisted of 662 men and women, and the
29 smallest cohort had only 58 individuals. Follow-up periods were not longer varying
30 from 6 months to 24 months, and the adjusted HR was displayed in four studies, and
31 one used OR and the other used RR. Table 2 shows the different tools and cutoff of
32 muscle mass, muscle strength and physical performance. Four studies used
33 bioelectrical impedance analysis (BAI) as a diagnostic criterion for muscle mass, and
34 the other two studies used anthropometric measures as diagnostic criteria.

49 **3.3 Quality assessment**

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51 The methodologic quality evaluation using NOS of all items is shown in Table 3.
52 The score of each study ranged from six to nine. The scores of five studies were more
53 than seven.

3.4 Sarcopenia as a predictor of mortality

3.4.1 Meta-analysis of studies

Six studies examined the association between sarcopenia and mortality among nursing home residents. The pooled HRs values were calculated by fixed-effects models. As show in Figure 2, the HRs of all-cause mortality for sarcopenia versus nonsarcopenia was 1.86 (95%CI=1.42-2.45, P=0.001). No significant heterogeneity was observed across these studies (Q-value=4.82, degree of freedom=5, $I^2=0\%$, $p=0.438$).

3.4.2 Subgroup analysis

The six studies with HR of all-cause mortality risks for sarcopenia among nursing home residents were further analysed by subgroup. Figure 3 compares all-cause mortality risk stratified by length of follow-up for sarcopeina. Two studies with a follow-up period less than 1 year for sarcopenia (pooled HR 1.85, 95%CI 0.95–3.60, $p=0.070$); whereas the analysis of other four studies had a follow-up period of 1 year or more (pooled HR 1.87,95%CI 1.38-2.52, $p=0.00$). Figure 4 shows sarcopenia was significantly associated with the risk of morbidity among nursing home residents when using BIA to diagnose muscle mass (pooled effect size=1.88,95% CI =1.39- 2.53, $p=0.00$), whereas it was not associated when using anthropometric measures to diagnosis muscle mass (pooled effect size=1.79,95% CI=0.89-3.59, $p=0.10$).

3.4.3 Publication bias assessment

There was no significant publication bias among the studies using Begg's test: $P=0.386$ (Figure 5).

3.4.4 sensitivity analysis of all studies.

We conducted a sensitivity analysis of sarcopenia and mortality by omitting one study each time and pooing the others to find which study would influence the main effect. No statistically significant changes were found, as shown in Figure 6.

4. Discussion

In this meta-analysis, we found evidence suggesting the risk of all-cause mortality among nursing home residents with sarcopenia was higher than that among nursing

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3 home residents without sarcopenia. To the best of our knowledge, this is the first
4 meta-analysis to explore the relationship between sarcopenia and all-cause mortality
5 among nursing home residents. Our study indicated assessing sarcopenia is really
6 important among the elderly that live in nursing homes.
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10 Ping Liu⁹ *et al.* implemented a systematic review and meta-analysis regarding the
11 association of sarcopenia with mortality in 2016, published in 2017. However, this
12 review included a population entirely of community-dwelling older people. So far,
13 Shu-Fang Chang³¹ and Beaudart³² both performed a systematic review to evaluate the
14 link between sarcopenia and all-cause mortality; however, there were some
15 methodologic shortcomings, such as various diagnostic criteria of sarcopenia, crude
16 ORs as effect, various population involving community-dwelling older people and
17 hospitalised patients. Although a subgroup of nursing home residents was analysed in
18 Beaudart's study, there is only two studies that was assessed, which maybe
19 underestimated or overestimated their result. Our review included six studies which
20 focus only on the association of mortality and sarcopenia in nursing home residents. the
21 results were stable and reliable after we tested the heterogeneity and publication bias
22 and performed sensitivity analysis among the included studies.
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34 This meta-analysis of six cohort studies shows sarcopenia is an important
35 predictor of all-cause mortality among nursing home residents. The pooled HR value of
36 all-cause mortality was 1.86 (95%CI=1.41-2.45, P=0.000, I² = 0%). The perfect I²
37 suggesting no significant heterogeneity was shown across these research. In addition,
38 our study's pooled HR value is higher than that of Ping Liu (1.60 95%CI: 1.24–2.06);
39 the primary reason was the different type of population. Those living in a nursing home
40 usually had worse health conditions and more comorbidities, more disability and more
41 geriatric syndromes, such as cognitive dysfunction and malnutrition^{17, 33-35}. This
42 comprehensive risk factor may aggravate the process of sarcopenia.
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51 The prevalence of sarcopenia was 32.8-73.3%, which is higher than that in other
52 studies. The difference was mainly due to the mean age, various population and
53 different diagnostic tools, particularly the ways researchers measured muscle mass.
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3 Sarcopenia was associated with all-cause mortality when using BIA to diagnose muscle
4 mass; whereas it was not associated when using anthropometric measures to diagnose
5 muscle mass. According to the EWGSOP¹, BIA is the most common tool for
6 diagnosing muscle mass; moreover, the test is inexpensive, easy to use, readily
7 reproducible and appropriate for both ambulatory and bedridden patients, which may
8 be considered a portable alternative to DXA (Dual Energy X-ray Absorptiometry) in
9 nursing homes. However, the method of anthropometric measures was based on
10 mid-upper-arm circumference and skin fold thickness³⁶; therefore, age-related changes
11 in fat deposits and loss of skin elasticity contribute to errors of estimation in older
12 nursing home residents, which are prone to produce errors³⁷. Furthermore,
13 anthropometric measures were not recommended for routine use in the diagnosis of
14 sarcopenia. The subgroup of length of follow-up analysis demonstrated that follow-up
15 period of 1 year or more was associated with all-cause mortality (pooled
16 HR=1.87,95%CI 1.38-2.52, p=0.000); however, it was not found with the follow-up
17 period of less than 1 year. The power for the short term analyses was too small to have
18 a significant result. Therefore, more perspective cohort studies about this issue must be
19 conducted in the future.

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The underlying mechanisms between sarcopenia and a higher risk of all-cause mortality were unable to draw conclusion; some aspects should be mentioned at least. Firstly, the association between sarcopenia and mortality may be explained by the hypothesised adverse effects of a low muscle mass in older people. Several studies showed that low muscle mass is highly associated with increased mortality³⁸⁻⁴⁰. In addition, elderly people in nursing homes are at high risk of malnutrition⁴¹, which aggravates low muscle mass, resulting in an increased mortality rate. Secondly, sarcopenia is linked to multiple factors ranging from aging process⁴², multiple chronic health conditions, unhealthy lifestyle⁴³, hormonal factors⁴⁴, inflammation⁴⁵ and so on⁴⁶. Meanwhile, the above factors are consider linked to mortality and the development of multifactor worsened the situation of sarcopenia, leading to a passive adaption to adversity or external stressors, which in turn generate increased poor adverse

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3 outcomes⁴⁷. Thirdly, according to the study of Fried⁴⁸ *et al.*, sarcopenia played a critical
4 etiologic role in the frailty process, which is related, through frailty, to pernicious
5 consequences—for instance, recurrent falls, bone fracture, disability, multiple
6 emergency room visits and hospital admissions and eventually death^{49, 50}. Moreover,
7 sarcopenia is considered to increase the risk of falls among the elderly⁵¹, and falls were
8 the major causes of death in nursing home residents⁵². Sarcopenia is a geriatric
9 syndrome rather than a disease; the mechanism of sarcopenia must be complex, which
10 needs more research to explore.
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18 Our meta-analysis review has multiple strengths and some limitations. One
19 strength was that we used an extensive search process in electronic databases and
20 assessed methodologic quality and tested the heterogeneity and publication bias among
21 the included studies. Another strength was that the included original studies were all of
22 prospective design, which minimized the possibility of recall bias and selection bias.
23 However, our study also has some limitations. Firstly, two included studies did not
24 directly report the HR in the sarcopenia group versus the non-sarcopenia group, but
25 used an approximation of OR to RR, and from RR to HR in the sarcopenia group, which
26 might not show an accurate HR value. Therefore, this approach may lead to method
27 heterogeneity. Another concern was that the cut-off for the muscle mass was different
28 in some studies, which will cause the prevalence of Sarcopenia to be various, thus
29 potentially influencing the result. Thirdly, the number of included studies in this
30 analysis was insufficient, and the sample size was relatively small. Fourthly, we
31 ignored the different adjusted confounding factors of the derived HR from different
32 studies. Fifthly, the language of studies was limited to English, and consequently we
33 may have missing data from important studies published in other languages, which may
34 result in potential language bias. In addition, the follow-up was relatively short for the
35 necessary latency, which may underestimate the results.
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51 **5. Conclusion**

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53 This study provides evidence that sarcopenia is a significant predictor of all-cause
54 mortality among nursing home residents based on the comprehensive systematic
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3 review and meta-analysis. Further studies are needed to provide evidence for specific
4 interventions to prevent and treat sarcopenia, which can reduce mortality in people
5 living in a nursing home.
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8 **6. Acknowledgements**

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11 hospital of Baoan ShenZhen for their guidance and support.
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17 not-for-profit sectors. No sponsors had any role in the design, methods, subject
18 recruitment, data collections, analysis or preparation of this manuscript.
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21 **8. Contributors**

22
23 Xiaoming Zhang was responsible for producing the initial draft of the manuscript.

24
25 Conghua Wang was responsible for data extraction and for producing the initial draft
26 of the manuscript.
27

28
29 Qingli Dou was responsible for data extraction.

30
31 Wenwu Zhang was responsible for screening the papers and quality assessment.

32
33 Xiaohua Xiewas responsible for screening the papers.

34
35 Yunzhi Yang was responsible for quality assessment, statistical analysis and revision
36 of the manuscript.
37

38
39 All the authors approved the final version of the manuscript

40 **9. Conflict of Interest**

41
42 None of the authors have any conflict of interest to declare.
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44 **10. Patient consent**

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46 Not required.

47 **10. Data Sharing Statements**

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49 All the data can be found in the electronic databases (PubMed, EMBASE, and the
50 Cochrane Library).
51

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Table 1 Summary of Included Studies on Sarcopenia Associated with All-cause Mortality

Author	Country	Year	Male	Sample number	Age of patients, years	Prevalence%	Follow-up period	mortality rate	Effect Measure	Adjusted or Crude HR/OR	Quality*
Saka B	Turkey	2015	51%	402	78.0±7.9	73.3	12 months	16.2%	HR	Adjusted	8
Yalcin A	Turkey	2017	54.3%	141	79.17±7.99	53.9	24 months	23.4%	HR	Age,sex,BMI,Calf circumference, MMSE,MNA, cerebrovascular diseases, osteoarthritis, chronic obstructive pulmonary disease, activity of daily living impairment, Diabetes, Dementia.	7
Landi F	Italy	2012	25%	122	84.1±4.8	32.8	6 months	21.3%	HRs	Age, sex, cerebrovascular diseases, osteoarthritis, chronic obstructive pulmonary disease,	8

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											Activity of daily living impairment	
Henwood T	Australia	2017	29.3%	58	85.7±8.2	51.7	18 months	21.6%	RR	Age, sex, BMI, MNA, physical activity	6	
Buckinx F	Belgium	2017	27.5%	662	83.2±8.99	36.2	12 months	15.9%	OR	Age, sex, BMI, Frailty, Waist circumference, Calf circumference, Arm circumference, Wrist circumference, Walking support, Drugs consumed, Medical history, MMSE, Minnesota ,MNA, Body fat,SF-36, EuroQol five dimensions, EuroQol-Visual Analogue Scale, Katz score, Fear of falling, Tinetti test, TUG test, SPPB test, Gait speed, Grip strength, Peak expiratory flow, Isometric strength	7	

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Kimyagarov	Israel	2012	41.2%	109	84.9±7.4	40.3	12 months	61.5%	HR	Age, sex, BMI	7
S										Charlson comorbidity index	

EWGSOP(European Working Group for Sarcopenia in Older Persons) defines sarcopenia in men as ALM adjusted for height squared <7.25 kg/m² combined with low hand-grip strength (<30 kg) and/or low gait speed(<0.8 m/s).

Quality* of the studies were assessed with Newcastle-Ottawa Scale(NOS); BMI: body mass index;MMSE: Mini-Mental State Examination; MNA:Mini-Nutritional Assessment; SF-36: Short Form Health Survey questionnaires; EuroQol five dimensions; EuroQol-Visual Analogue Scale;Tinetti test;TUG test: Timed Up and Go;SPPB test: Short physical performance battery

Table 2 Study and Sarcopenia criteria

study	Sarcopenia criteria	Item, tool, Cutoff points	Muscle mass	Muscle strength	Physical performance	Ref		
		Tool	Cutoff points	Tool	Cutoff points	Tool	Cutoff point	
Yalcin A 2017	EWFSOP	BIA	Men: SMI $\leq 8.87 \text{ Kg/m}^2$ Women: SMI $\leq 6.42 \text{ Kg/m}^2$	handgrip strength	Men: HGS $< 30 \text{ Kg}$ Women: HGS $< 20 \text{ Kg}$	Gait speed: 4-m	$\leq 0.8 \text{ m/s}$	18
Buckinx F 2017	EWFSOP	BIA	Men: SMI $\leq 8.87 \text{ Kg/m}^2$ Women: SMI $\leq 6.42 \text{ Kg/m}^2$	Handgrip strength	None	SPPB: Short Physical Performance Battery	$\leq 0.8 \text{ m/s}$	14
Henwood T	EWFSOP	BIA	Men: SMI $< 8.87 \text{ kg/m}^2$ Women: SMI $< 6.42 \text{ kg/m}^2$	hand grip Strength	Men: HGS $< 30 \text{ Kg}$ Women: HGS $< 20 \text{ Kg}$	SPPB: Short Physical Performance Battery	$\leq 0.8 \text{ m/s}$	16
Saka B	EWFSOP	anthropometric measures	CC $< 31 \text{ cm}$ in men and women MuAMC $< 23.8 \text{ cm}$ in men MUAMC $< 23.3 \text{ cm}$ in women	hand grip Strength	Men: HGS $< 30 \text{ Kg}$ Women: HGS $< 20 \text{ Kg}$	Gait speed: 4-m	$\leq 0.8 \text{ m/s}$	17
Kimyagarov S	NIH-sponsored workshop	anthropometric measures	SMM index: (males) $< 10.5 \text{ kg/m}^2$ (females) $< 8.5 \text{ kg/m}^2$	manual muscle testing	MMT* score < 106	None	None	19

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LandiF	EWFSOP	BIA	Men:SMI <8.87 kg/m ²	hand grip	Men:HGS <30Kg	Gait speed: 4-m	≤ 0.8 m/s	15
			Women:SMI <6.42 kg/m ²	Strength	Women:HGS <20Kg			

MMT*: an isometric semi-quantitative measurement of eight limb muscles groups, in which muscle strength has subjective grades. On the classic 0 to 5-point scale, the lowest grade (0) indicates no contractility or muscle activation, and the highest possible grade (160 points) represents full resistance.

Table 3
Result of the Newcastle-Ottawa scale quality assessment

Newcastle-Ottawa scale		Saka B 2015	Yalcin A 2017	LandiF 2012	Kimyagarov S 2012	Henwood T 2017	Buckinx F 2017
Selection(4)	Representativeness of the exposed cohort	1	1	1	1	1	1
	Selection of the non-exposed cohort	1	1	1	1	1	1
	Ascertainment of exposure	1	1	1	1	1	1
	Demonstration that outcome of interest was not present at start of study	1	1	1	1	1	1
Comparability(2)	Comparability of cohorts on the basis of the design or analysis	2	1	2	1	1	2
Outcome(3)	Assessment of outcome	1	1	1	1	1	1
	Was follow-up long enough for	0	0	0	0	0	0

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	outcome to occur						
	Adequacy of follow up of cohorts	1	1	1	1	1	1
Quality(9)	Total	8	7	8	7	6	7

For peer review only

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3 Figure 1. The flow diagram of studies selection.

4 Figure 2. Meta-analysis of the association between sarcopenia and mortality among older nursing
5 home residents.

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7 Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up.

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9 Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle
10 mass.

11 Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents.

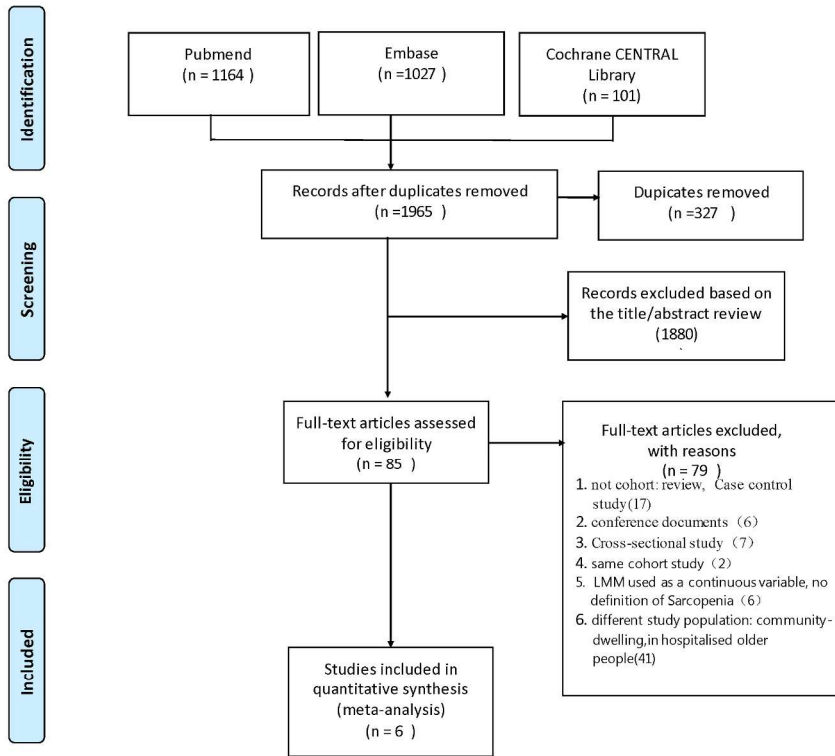
12
13 Figure 6. Sensitivity analysis of all studies.
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Figure 1. The flow diagram of studies selection.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1. The flow diagram of studies selection.

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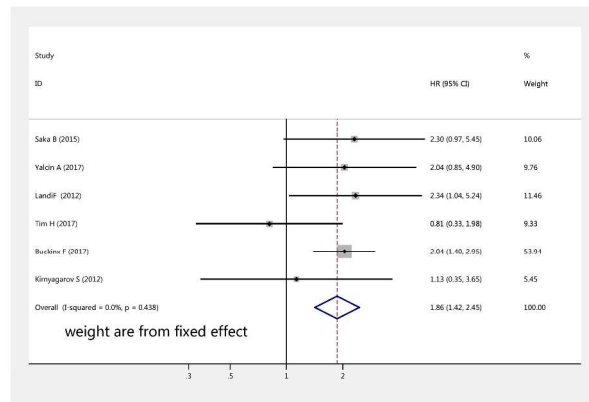


Figure 2. Meta-analysis of the association between Sarcopenia and mortality

Figure 2. Meta-analysis of the association between Sarcopenia and mortality

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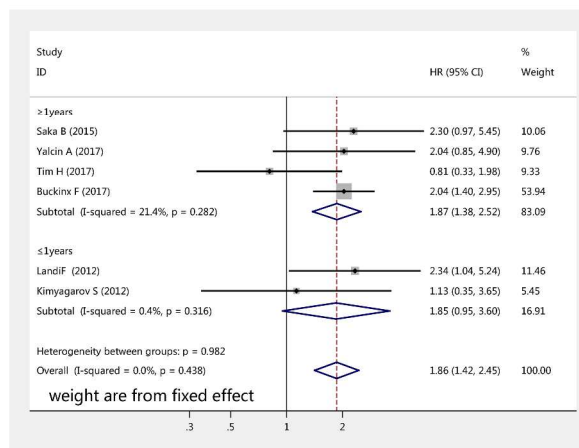


Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

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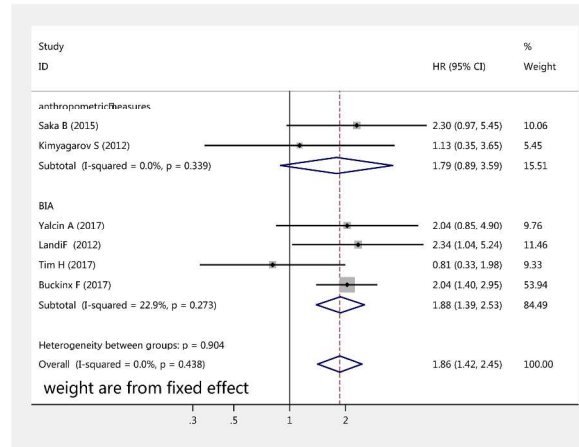


Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

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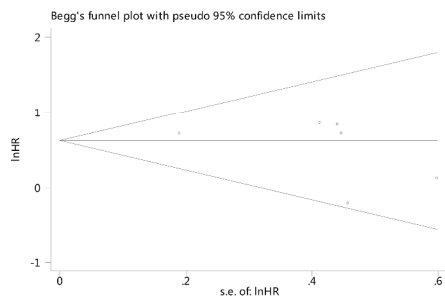


Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

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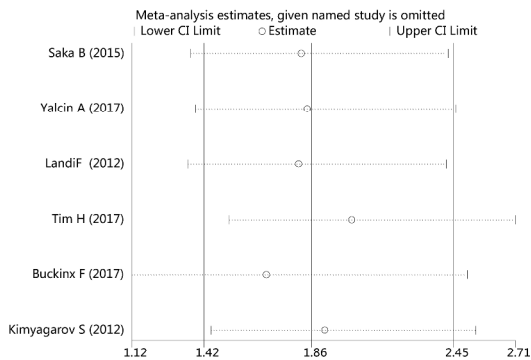


Figure.6 Sensitivity analysis of all studies.

Figure.6 Sensitivity analysis of all studies.

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9 #5: Search mortality*
10 #6: Search "Death"[Mesh]
11 #7: Search death*
12 #8: Search survival*
13 #9: Search "Survival"[Mesh]
14 #10: Search (((("Survival"[Mesh]) OR survival*) OR death*) OR "Death"[Mesh]) OR mortality*) OR
15 "Mortality"[Mesh]
16 #11: Search ((((((("Survival"[Mesh]) OR survival*) OR death*) OR "Death"[Mesh]) OR mortality*)
17 OR "Mortality"[Mesh])) AND (("Sarcopenia"[Mesh]) OR sarcopenia*)
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25 #1: Search sarcopenia*
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27 #3: #1OR #2
28 #4: Search MeSH descriptor: [mortality] explode all trees
29 #5: Search mortality*
30 #6: Search MeSH descriptor: [death] explode all trees
31 #7: Search death*
32 #8: Search survival*
33 #9: Search MeSH descriptor: [survival] explode all trees
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41 EMBASE

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MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	3
4	Type of exposure or intervention used	3
5	Type of study designs used	3
6	Study population	4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	None
8	Search strategy, including time period included in the synthesis and key words	4
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	4
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	4
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	7
26	Table giving descriptive information for each study included	7
27	Results of sensitivity testing (eg, subgroup analysis)	8
28	Indication of statistical uncertainty of findings	None

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	9
30	Justification for exclusion (eg, exclusion of non-English language citations)	9
31	Assessment of quality of included studies	None
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	11
34	Guidelines for future research	11
35	Disclosure of funding source	12

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Sarcopenia as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis

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3 **Sarcopenia as a predictor of all-cause mortality among older nursing home**
4 **residents: a systematic review and meta-analysis**
5

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Abstract

Objectives: This study aims to review the evidence of sarcopenia as a predictor of all-cause mortality among nursing home residents.

Design: systematic review and meta-analysis of observational cohort studies

Data sources: PubMed, EMBASE, and the Cochrane Library databases were searched for relevant articles.

Participants: Nursing home residents.

Primary and secondary outcome measures: All-cause mortality

Data analysis: Summary-adjusted hazard ratios (HRs) or risk ratios (RRs) were calculated by fixed-effects model. The risk of bias was assessed by Newcastle-Ottawa Scale.

Results: Of 2,292 studies identified through the systematic review, six studies (1494 participants) were included in the meta-analysis. Sarcopenia was significantly associated with a higher risk for all-cause mortality among nursing home residents (pooled HR=1.86, 95% confidence interval [95% CI] =1.42-2.45, $p<0.001$, $I^2=0$). In addition, the subgroup analysis demonstrated that sarcopenia was associated with all-cause mortality (pooled HR 1.87, [95%CI] =1.38- 2.52, $p<0.001$) when studies with a follow-up period of 1 year or more were analysed; however, this was not found for studies with the follow-up period less than 1 year. Furthermore, sarcopenia was significantly associated with the risk of mortality among older nursing home residents when using bioelectrical impedance analysis (BIA) to diagnosis muscle mass (pooled HR=1.88, 95% CI = 1.39- 2.53, $p<0.001$); whereas, it was not found when anthropometric measures was used to diagnosis muscle mass.

Conclusion: Sarcopenia is a significant predictor of all-cause mortality among older nursing home residents. Therefore, it is important to diagnose and treat sarcopenia to reduce mortality rates among nursing home residents.

PROSPEERO registration number: CRD42018081668

Key words: Sarcopenia; All-cause mortality; Nursing Home; Meta-analysis

Strengths and limitations of this study

1. To the best of our knowledge, it is the first meta-analysis to explore the relationship between sarcopenia and all-cause mortality among elderly nursing home residents.
2. An extensive search process in an electronic database was used and methodological quality was assessed; we also tested the heterogeneity and publication bias and performed sensitivity analysis among the included studies.
3. This systematic review and meta-analysis assessed the overall quality of the evidence by using Newcastle Ottawa Scale (NOS) approach for prospective observational studies and conducted a meta-analysis and subgroup analysis.
4. The number of studies included in this analysis were insufficient, and the size sample was relatively small.
5. Different cutoff values for the muscle mass might affect the relationship between sarcopenia and all-cause mortality.

1. Introduction

Sarcopenia is a common syndrome characterised by a loss of muscle mass and strength with functional impairment and adverse health outcomes due to cumulative deficits of multiple systems¹. Nursing home residents are at a particularly high risk for sarcopenia². According to studies, the prevalence of sarcopenia was 1-29% for community-dwelling older adults, 14–85.4% in nursing homes²⁻⁴ and 10-24.3% for those in hospitals⁵. Sarcopenia leads to a worse outcome in elderly people, including physical disability, falls, fractures, poor quality of life, mortality and hospitalisation⁶⁻⁸. Among these, mortality might be considered the most important outcome in elderly people. So far, the relationship between mortality and operational criteria that define sarcopenia has been well described in community-dwelling older adults and hospitalised patients. A recent meta-analysis study, Liu⁹ *et al.*, analysed sarcopenia and mortality and concluded that sarcopenia is a predictor of all-cause mortality among

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3 community-dwelling older people. However, there is no consistent conclusion
4 regarding the relationship between sarcopenia and mortality among nursing home
5 residents. It has been shown that the mortality rate in nursing homes¹⁰ is approximately
6 2-fold higher than that in the community¹¹⁻¹³; therefore, it is very important to confirm
7 the risk factors for mortality among nursing home residents.
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12 Several studies found that elderly people with sarcopenia were predictors of
13 all-cause mortality among nursing home residents^{14, 15}. However, some studies did not
14 find any significant relationship between sarcopenia and all-cause mortality¹⁶⁻¹⁹. Given
15 the observed contradictory relationship between sarcopenia and all-cause mortality
16 among nursing home residents in some studies, further studies are needed. However, no
17 systematic reviews of meta-analysis studies on this topic have been conducted in the
18 literature. Therefore, our study aims to identify and compare prospective cohort studies
19 examining sarcopenia as a predictor of all-cause mortality among nursing home
20 residents according to the MOOSE guidelines
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29 **2. Materials and methods**

30 This meta-analysis was registered with the international prospective Register for
31 Systemic Reviews (CRD42018081668) and conducted according to the MOOSE
32 guidelines²⁰.
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36 **2.1. Search strategy and selection criteria**

37 A systematic literature search was conducted in MEDLINE (via PubMed 1946 to
38 November 2017), EMBASE (via EMBASE November 2017) and Cochrane
39 CENTRAL Library (via Cochrane Library November 2017). The search strategy was
40 tailored according to each database. We used a combination of key words such as
41 mortality (mortality*), OR death (death*), OR survival (survival*) and sarcopenia
42 (sarcopenia*), as well as MeSH terms. We also used subject terms and truncation
43 symbols in our search strategy. We searched the potential grey studies through Google
44 Scholar. Furthermore, we carried out a manual search on the references of included
45 studies. The full search strategy for three databases has been provided as a
46 supplementary file.
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2.2. Study selection

These studies which was identified by our search strategy were reviewed by teams of two independently blinded investigators (Zhang XM and Wang CH) who evaluated each title and abstract. In case of disagreement (whether to include or exclude studies), the issue was discussed and a third reviewer evaluated the study until the reviewers reached consensus.

2.3. Inclusion and exclusion criteria

The following eligibility and exclusion criteria were prespecified. Studies had to fulfil the following four inclusion criteria: (1) prospective cohort studies, (2) studies investigating whether sarcopenia was a predictor of mortality, (3) studies reporting clear diagnostic criteria for sarcopenia, (4) type of participant: elderly adult in nursing home or nursing care. Exclusion criteria were as follows: (1) Type of participant: community-dwelling older people (aged 65 years or older) or hospitalised older people; (2) article type: only abstract, letters and laboratory research; review articles; (3) insufficient data; (4) other languages of studies, except English; (5) no clear definition of sarcopenia.

2.4. Data extraction

Two investigators (Zhang XM, Wang CH) independently abstracted the data from the selected studies using a standardised data-abstraction form. The following information was extracted from included papers: author, country, year of publication, demographic characteristics of participants (e.g., sample size, male proportion), measurement methods of sarcopenia, follow-up period, Adjusted variable, and study quality. The reviewers cross-checked all extracted data. Disagreements were resolved by discussion until consensus was reached.

2.5. Assessment of risk bias

Assessment of risk of bias was performed by two independent reviewers (Zhang XM, Wang CH) according to the Newcastle Ottawa Scale (NOS)²¹: (1) representativeness of the exposed cohort, (2) comparability of group, (3) blinding of investigators who measured outcomes, (4) the time and completeness of follow-up, (5)

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3 contamination bias, and (6) other potential sources of bias. The total score of the scale is
4 9 points. When the total score is ≥ 5 points, it is considered as a high-quality research.

6 **2.6. Statistical analysis**

8 The STATA version 14.0 (Stata Corp., College Station, TX, USA) was
9 independently used for all analyses by two authors (Zhang XM, Dou QL). Hazard ratios
10 (HRs), odds ratio (ORs) and their 95% CIs of mortality for sarcopenia compared with
11 non-sarcopenia were extracted from studies for future meta-analysis. RR was
12 considered equivalent to HR in our prospective cohort studies, which was reported in
13 Carole Willi's²² study and Ahmed N Mahmoud's study²³. If a study reported the effect
14 size as an OR, it was converted to RR using a previously described formula²⁴. All the
15 effect of HR or RR was converted to $\ln(\text{HR})$ or $\ln(\text{RR})$ for ratio in meta-analysis,
16 Subgroup analyses were conducted by different diagnosis tools for muscle mass and
17 follow-up period if there was more than one study in the subgroup. The statistical
18 heterogeneity among the included studies was examined with Cochran's Q statistic
19 using chi-square and I^2 statistics, and I^2 value of 25%, 50% and 75% represented the
20 cut-off of low, moderate and high heterogeneity, respectively. If heterogeneity was
21 found to be reasonably high between studies, the random-effects model was used.
22 Otherwise, the fixed-effects model was used. Results were illustrated using forest plots,
23 and Begg's Test was done to plot the log HR against its standard error for assessment of
24 potential publication bias.

39 **2.7. Patient and Public Involvement**

40 The patients or public were not involved in the study.

43 **3. Results**

45 **3.1. Search results**

46 The literature search strategy initially identified 2,292 articles. After removal of
47 duplicates, 1,965 articles were screened for potential eligibility. A total of 85
48 publications remained for further consideration. Then we screened titles and abstracts
49 and removed unrelated articles. Of these articles, 30 were removed because of non-
50 cohort studies (e.g., review articles, conference documents, cross-sectional study,
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3 case-control study), and six were removed because they had no clear definition of
4 sarcopenia; moreover, 41 were removed on account of different study population:
5 community-dwelling older people, patients in hospital, and used the same cohorts (n =
6 2). These studies were screened according to the predefined inclusion and exclusion
7 criteria for inclusion in the meta-analysis, resulting in a total of six eligible studies
8 (Figure 1).
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14 3.2 Included studies

16 Six prospective cohort studies were included in our meta-analysis with 1,494 total
17 participants. Study characteristics of included papers are displayed in table 1. Two
18 studies were conducted in Turkey^{25, 26}, one study in Italy²⁷⁻²⁹, one study in Australia³⁰,
19 one study in Belgium and one study in Israel. All the studies selected all-cause
20 mortality as the clinical outcome and five studies used the sarcopenia criteria of
21 European Working Group for Sarcopenia (EWGSOP), the other used NIH-sponsored
22 workshop³¹ to diagnose sarcopenia. The EWGSOP¹ recommends using the presence of
23 both low muscle function (strength or performance) and low muscle mass for the
24 diagnosis of sarcopenia. Thus, diagnosis of sarcopenia in the present study required the
25 documentation of low muscle mass plus the documentation of either low muscle
26 strength or low physical performance. The prevalence of sarcopenia ranged from 32.8
27 to 73.3%. The largest study consisted of 662 men and women, and the smallest cohort
28 had only 58 individuals. Follow-up periods were no longer varying from 6 months to 24
29 months, and the adjusted HR was displayed in four studies, and one used OR and the
30 other used RR. Table 2 shows the different tools and cut-off of muscle mass, muscle
31 strength and physical performance. Four studies used bioelectrical impedance analysis
32 (BAI) as a diagnostic criterion for muscle mass, and the other two studies used
33 anthropometric measures as diagnostic criteria.
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49 3.3 Quality assessment

51 The methodological quality evaluation using NOS of all items is shown in Table 3.
52 The score of each study ranged from six to nine. The scores of five studies were more
53 than seven.
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3.4 Sarcopenia as a predictor of mortality

3.4.1 Meta-analysis of studies

Six studies examined the association between sarcopenia and mortality among nursing home residents. The pooled HRs values were calculated by fixed-effects models. As show in Figure 2, the HRs of all-cause mortality for sarcopenia versus non-sarcopenia was 1.86 (95%CI=1.42-2.45, $p<0.001$). No significant heterogeneity was observed across these studies (Q-value=4.82, degree of freedom=5, $I^2=0\%$, $p=0.438$).

3.4.2 Subgroup analysis

The six studies with HR of all-cause mortality risks for sarcopenia among nursing home residents were further analysed by subgroup. Figure 3 compares all-cause mortality risk stratified by length of follow-up for sarcopenia. Two studies that followed up 231 cases for a period of less than 1 year (pooled HR 1.85, 95%CI 0.95–3.60, $p=0.070$); whereas the analysis of other four studies that followed up 1263 cases for a period of 1 year or more (pooled HR 1.87, 95%CI 1.38-2.52, $p<0.001$). Figure 4 shows sarcopenia was significantly associated with the risk of mortality among nursing home residents when using bioelectrical impedance analysis (BIA) to diagnose muscle mass (pooled effect size=1.88,95% CI =1.39- 2.53, $p<0.001$), whereas it was not associated when using anthropometric measures to diagnosis muscle mass (pooled effect size=1.79,95% CI=0.89-3.59, $p=0.100$).

3.4.3 Publication bias assessment

There was no significant publication bias among the studies using Begg's test: $p=0.386$ (Figure 5).

3.4.4 Sensitivity analysis of all studies.

We conducted a sensitivity analysis of sarcopenia and mortality by omitting one of the included studies each time, and poing the others together to find which study would influence the main pooled HR. No statistically significant changes were found, as shown in Figure 6.

4. Discussion

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3 In this meta-analysis, we found evidence suggesting the risk of all-cause mortality
4 among nursing home residents with sarcopenia was higher than that among nursing
5 home residents without sarcopenia. To the best of our knowledge, this is the first
6 meta-analysis to explore the relationship between sarcopenia and all-cause mortality
7 among nursing home residents. Our study indicated assessing sarcopenia is really
8 important among the elderly that live in nursing homes.
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14 Ping Liu⁹ *et al.* implemented a systematic review and meta-analysis regarding the
15 association of sarcopenia with mortality in 2016, published in 2017. However, this
16 review included a population entirely of community-dwelling older people. So far,
17 Shu-Fang Chang³² and Beaudart³³ both performed a systematic review to evaluate the
18 link between sarcopenia and all-cause mortality; however, there were some
19 methodological shortcomings, such as various diagnostic criteria of sarcopenia, crude
20 ORs as effect, various population involving community-dwelling older people and
21 hospitalised patients. Although a subgroup of nursing home residents was analysed in
22 Beaudart's study, there is only two studies that was assessed, which maybe
23 underestimated or overestimated their result. Our review included six studies which
24 focus only on the association of mortality and sarcopenia in nursing home residents.
25 The results were stable and reliable after we tested the heterogeneity and publication
26 bias and performed sensitivity analysis among the included studies.
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38 This meta-analysis of six cohort studies shows sarcopenia is an important
39 predictor of all-cause mortality among nursing home residents. The pooled HR value of
40 all-cause mortality was 1.86 (95%CI=1.41-2.45, $p<0.001$, $I^2 = 0\%$). The small I^2
41 suggesting no significant heterogeneity was shown across these studies. In addition, our
42 study's pooled HR value is higher than that of Ping Liu⁹ (1.60 95%CI: 1.24–2.06); the
43 primary reason was the different type of population. Those living in a nursing home
44 usually had worse health conditions and more comorbidities, more disability and more
45 geriatric syndromes, such as cognitive dysfunction and malnutrition^{17, 34-36}. This
46 comprehensive risk factor may aggravate the process of sarcopenia.
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54 In our present study, the prevalence of sarcopenia varied from 32.8-73.3%. The
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3 difference was mainly due to the mean age, various population and different diagnostic
4 tools, particularly the ways that researchers measured muscle mass. A previous study
5 showed that sarcopenia was associated with mortality when BIA was used to diagnose
6 muscle mass³⁷. In this present study, we confirmed that sarcopenia was associated with
7 all-cause mortality using BIA to diagnose muscle mass; however, the association was
8 not found when using anthropometric measures. According to the EWGSOP¹, BIA is
9 the most common tool for diagnosing muscle mass; moreover, the test is inexpensive,
10 easy to use, readily reproducible and appropriate for both ambulatory and bedridden
11 patients, which may be considered a portable alternative to DXA (Dual Energy X-ray
12 Absorptiometry) in nursing homes. However, the method of anthropometric measures
13 was based on mid-upper-arm circumference and skin fold thickness³⁸; therefore,
14 age-related changes in fat deposits and loss of skin elasticity contribute to errors of
15 estimation in older nursing home residents, which are prone to produce errors³⁹.
16 Furthermore, anthropometric measures were not recommended for routine use in the
17 diagnosis of sarcopenia.
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31 It has been demonstrated that length follow-up could influence the association
32 between sarcopenia and mortality⁹. Our study showed that the subgroup of length of
33 follow-up analysis demonstrated that follow-up period of 1 year or more was associated
34 with all-cause mortality (pooled HR=1.87, 95%CI 1.38-2.52, p<0.001); however, it was
35 not found with the follow-up period of less than 1 year (pooled HR=1.85, 95%CI
36 0.95-3.60, p=0.070). It is noticed that there were only 231 cases in the two studies with
37 the follow-up period of less than 1 year and it is likely that the numbers of studies and
38 included cases for short term analysis were too small to have a significant result.
39 Therefore, more perspective cohort studies about this issue must be conducted in the
40 future.
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49 The underlying mechanisms between sarcopenia and a higher risk of all-cause
50 mortality were unable to draw a conclusion; some aspects should be mentioned at least.
51 Firstly, the association between sarcopenia and mortality may be explained by the
52 hypothesised adverse effects of a low muscle mass in older people. Several studies
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3 showed that low muscle mass is highly associated with increased mortality⁴⁰⁻⁴². In
4 addition, elderly people in nursing homes are at high risk of malnutrition⁴³, which
5 aggravates low muscle mass, resulting in an increased mortality rate. Secondly,
6 sarcopenia is linked to multiple factors ranging from aging process⁴⁴, multiple chronic
7 health conditions, unhealthy lifestyle⁴⁵, hormonal factors⁴⁶, inflammation⁴⁷ and so on⁴⁸.
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9 Meanwhile, the above factors are considered to be linked with mortality and the
10 development of multifactor worsened the situation of sarcopenia, leading to a passive
11 adaption to adversity or external stressors, which in turn generate increased poor
12 adverse outcomes⁴⁹. Thirdly, according to the study of Fried⁵⁰ *et al.*, sarcopenia played
13 a critical etiologic role in the frailty process, which is related, through frailty, to
14 pernicious consequences, for instance, recurrent falls, bone fracture, disability,
15 multiple emergency room visits and hospital admissions and eventually death^{51, 52}.
16 Moreover, sarcopenia is considered to increase the risk of falls among the elderly⁵³, and
17 falls were the major causes of death in nursing home residents⁵⁴. Sarcopenia is a
18 geriatric syndrome rather than a disease; the mechanism of sarcopenia is very complex,
19 which needs more research to explore.
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32 Our meta-analysis review has multiple strengths and some limitations. One
33 strength was that we used an extensive search process in electronic databases and
34 assessed methodological quality and tested the heterogeneity and publication bias
35 among the included studies. Another strength was that the included original studies
36 were all of prospective design, which minimized the possibility of recall bias and
37 selection bias. However, our study also has some limitations. Firstly, two included
38 studies did not directly report the HR in the sarcopenia group versus the non-sarcopenia
39 group, but used an approximation of OR to RR, and from RR to HR in the sarcopenia
40 group, which might not show an accurate HR value. Therefore, this approach may lead
41 to method heterogeneity. Another concern was that the cut-off for the muscle mass was
42 different in some studies, which caused the prevalence of Sarcopenia to be various, thus
43 potentially influenced the result. Thirdly, the number of included studies in this
44 analysis was insufficient, and the sample size was relatively small. Fourthly, we
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3 ignored the different adjusted confounding factors of the derived HR from different
4 studies. Fifthly, the language of studies was limited to English, and consequently some
5 data from important studies published in other languages have been ignored, which
6 may result in potential language bias. In addition, the follow-up was relatively short for
7 the necessary latency, which may underestimate the results.
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12 **5. Conclusion**

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14 This study provides evidence that sarcopenia is a significant predictor of all-cause
15 mortality among nursing home residents based on the comprehensive systematic
16 review and meta-analysis. Further studies need to be provided with evidence for
17 specific interventions to prevent and treat sarcopenia, which can reduce mortality in
18 people living in a nursing home.
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23 **6. Acknowledgements**

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26 hospital of Baoan, Shenzhen for their guidance and support.
27
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30
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32 not-for-profit sectors. No sponsors had any role in the design, methods, subject
33 recruitment, data collections, analysis or preparation of this manuscript.
34
35

36 **8. Contributors**

37
38 Xiaoming Zhang was responsible for producing the initial draft of the manuscript.

39
40 Conghua Wang was responsible for data extraction and for producing the initial
41 draft of the manuscript.
42

43
44 Qingli Dou was responsible for data extraction.

45
46 Wenwu Zhang was responsible for screening the papers and quality assessment.

47
48 Xiao Hua Xie was responsible for screening the papers.

49
50 Yunzhi Yang was responsible for quality assessment, statistical analysis and
51 revision of the manuscript.
52

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54 All the authors approved the final version of the manuscript

55 **9. Conflict of Interest**

None of the authors have any conflict of interest to declare.

10. Patient consent

Not required.

10. Data Sharing Statements

All the data can be found in the electronic databases (PubMed, EMBASE, and the Cochrane Library).

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Table 1 Summary of Included Studies on Sarcopenia Associated with All-cause Mortality

Author	Country	Year	Male	Sample number	Age of patients, years	Prevalence%	Follow-up period	mortality rate	Effect Measure	Adjusted or Crude HR/OR	Quality*
Saka B	Turkey	2015	51%	402	78.0±7.9	73.3	12 months	16.2%	HR	Adjusted	8
Yalcin A	Turkey	2017	54.3%	141	79.17±7.99	53.9	24 months	23.4%	HR	Age, sex, BMI, Calf circumference, MMSE, MNA, cerebrovascular diseases, osteoarthritis, chronic obstructive pulmonary disease, activity of daily living impairment, Diabetes, Dementia.	7
Landi F	Italy	2012	25%	122	84.1±4.8	32.8	6 months	21.3%	HRs	Age, sex, cerebrovascular diseases, osteoarthritis, chronic obstructive pulmonary disease,	8

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											Activity of daily living impairment	
Henwood T	Australia	2017	29.3%	58	85.7±8.2	51.7	18 months	21.6%	RR	Age, sex, BMI, MNA, physical activity	6	
Buckinx F	Belgium	2017	27.5%	662	83.2±8.99	36.2	12 months	15.9%	OR	Age, sex, BMI, Frailty, Waist circumference, Calf circumference, Arm circumference, Wrist circumference, Walking support, Drugs consumed, Medical history, MMSE, Minnesota ,MNA, Body fat,SF-36, EuroQol five dimensions, EuroQol-Visual Analogue Scale, Katz score, Fear of falling, Tinetti test, TUG test, SPPB test, Gait speed, Grip strength, Peak expiratory flow, Isometric strength	7	

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Kimyagarov	Israel	2012	41.2%	109	84.9±7.4	40.3	12 months	61.5%	HR	Age, sex, BMI	7
S										Charlson comorbidity index	

EWGSOP(European Working Group for Sarcopenia in Older Persons) defines sarcopenia in men as ALM adjusted for height squared <7.25 kg/m² combined with low hand-grip strength (<30 kg) and/or low gait speed(<0.8 m/s).

Quality* of the studies were assessed with Newcastle-Ottawa Scale(NOS); BMI: body mass index;MMSE: Mini-Mental State Examination; MNA: Mini-Nutritional Assessment; SF-36: Short Form Health Survey questionnaires; EuroQol five dimensions; EuroQol-Visual Analogue Scale; Tinetti test; TUG test: Timed Up and Go; SPPB test: Short physical performance battery

Table 2 Study and Sarcopenia criteria

study	Sarcopenia criteria	Item, tool, Cutoff points	Muscle mass	Muscle strength	Physical performance	Ref		
		Tool	Cutoff points	Tool	Cutoff points	Tool	Cutoff point	
Yalcin A 2017	EWFSOP	BIA	Men: SMI $\leq 8.87 \text{ Kg/m}^2$ Women: SMI $\leq 6.42 \text{ Kg/m}^2$	handgrip strength	Men: HGS $< 30 \text{ Kg}$ Women: HGS $< 20 \text{ Kg}$	Gait speed: 4-m	$\leq 0.8 \text{ m/s}$	18
Buckinx F 2017	EWFSOP	BIA	Men: SMI $\leq 8.87 \text{ Kg/m}^2$ Women: SMI $\leq 6.42 \text{ Kg/m}^2$	Handgrip strength	None	SPPB: Short Physical Performance Battery	$\leq 0.8 \text{ m/s}$	14
Henwood T	EWFSOP	BIA	Men: SMI $< 8.87 \text{ kg/m}^2$ Women: SMI $< 6.42 \text{ kg/m}^2$	hand grip Strength	Men: HGS $< 30 \text{ Kg}$ Women: HGS $< 20 \text{ Kg}$	SPPB: Short Physical Performance Battery	$\leq 0.8 \text{ m/s}$	16
Saka B	EWFSOP	anthropometric measures	CC $< 31 \text{ cm}$ in men and women MuAMC $< 23.8 \text{ cm}$ in men MUAMC $< 23.3 \text{ cm}$ in women	hand grip Strength	Men: HGS $< 30 \text{ Kg}$ Women: HGS $< 20 \text{ Kg}$	Gait speed: 4-m	$\leq 0.8 \text{ m/s}$	17
Kimyagarov S	NIH-sponsored workshop	anthropometric measures	SMM index: (males) $< 10.5 \text{ kg/m}^2$ (females) $< 8.5 \text{ kg/m}^2$	manual muscle testing	MMT* score < 106	None	None	19

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LandiF	EWFSOP	BIA	Men:SMI <8.87 kg/m ²	hand grip	Men:HGS <30Kg	Gait speed: 4-m	≤ 0.8 m/s	15
			Women:SMI <6.42 kg/m ²	Strength	Women:HGS <20Kg			

MMT*:an isometric semi-quantitative measurement of eight limb muscles groups, in which muscle strength has subjective grades.
 On the classic 0 to 5-point scale, the lowest grade (0) indicates no contractility or muscle activation,
 and the highest possible grade (160 points) represents full resistance.

Table 3
 Result of the Newcastle-Ottawa scale quality assessment

Newcastle-Ottawa scale		Saka B 2015	Yalcin A 2017	LandiF 2012	Kimyagarov S 2012	Henwood T 2017	Buckinx F 2017
Selection(4)	Representativeness of the exposed cohort	1	1	1	1	1	1
	Selection of the non-exposed cohort	1	1	1	1	1	1
	Ascertainment of exposure	1	1	1	1	1	1
	Demonstration that outcome of interest was not present at start of study	1	1	1	1	1	1
Comparability(2)	Comparability of cohorts on the basis of the design or analysis	2	1	2	1	1	2
Outcome(3)	Assessment of outcome	1	1	1	1	1	1
	Was follow-up long enough for	0	0	0	0	0	0

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	outcome to occur						
	Adequacy of follow up of cohorts	1	1	1	1	1	1
Quality(9)	Total	8	7	8	7	6	7

For peer review only

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3 Figure 1. The flow diagram of studies selection.

4 Figure 2. Meta-analysis of the association between sarcopenia and mortality among older nursing
5 home residents.

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7 Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up.

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9 Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle
10 mass.

11 Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents.

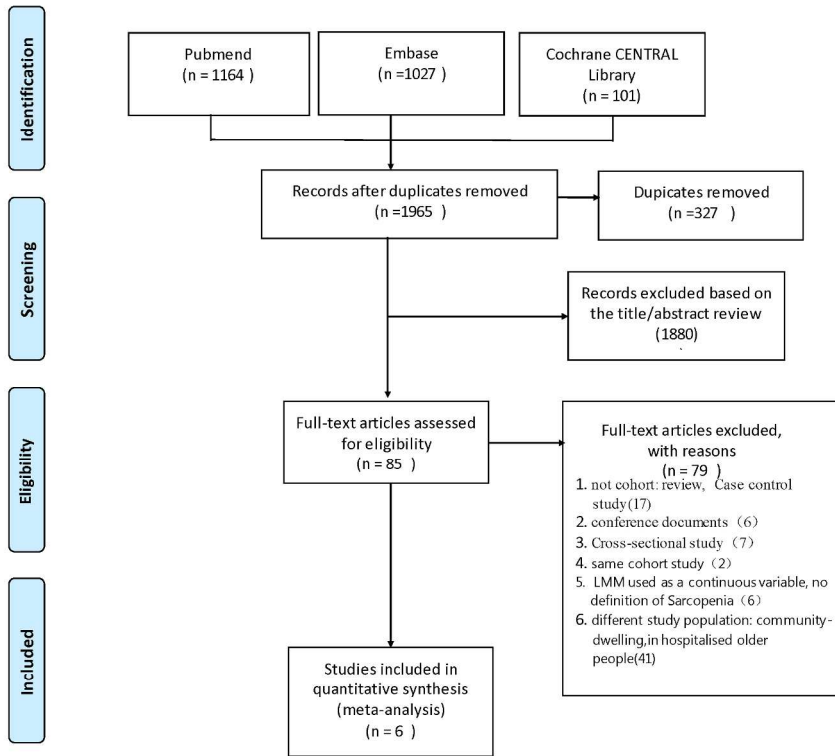
12
13 Figure 6. Sensitivity analysis of all studies.
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Figure 1. The flow diagram of studies selection.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1. The flow diagram of studies selection.

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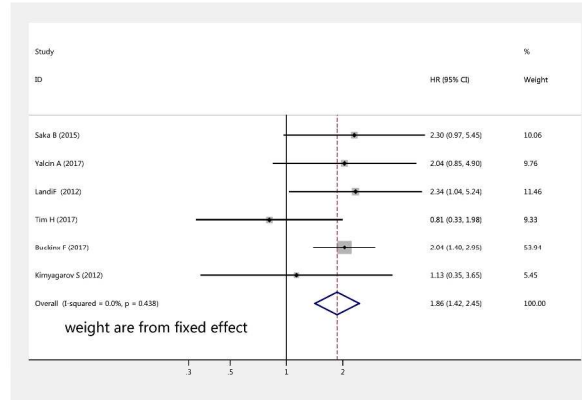


Figure 2. Meta-analysis of the association between Sarcopenia and mortality

Figure 2. Meta-analysis of the association between Sarcopenia and mortality

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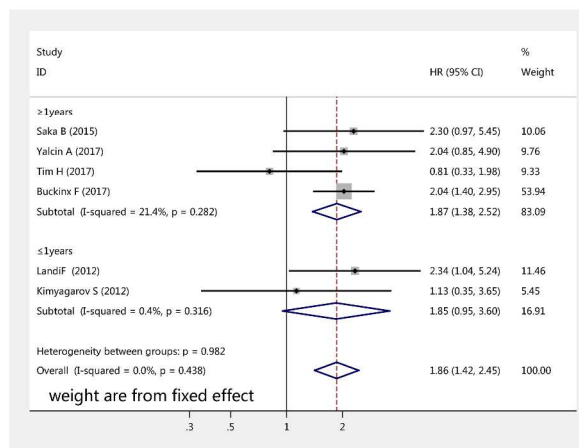


Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

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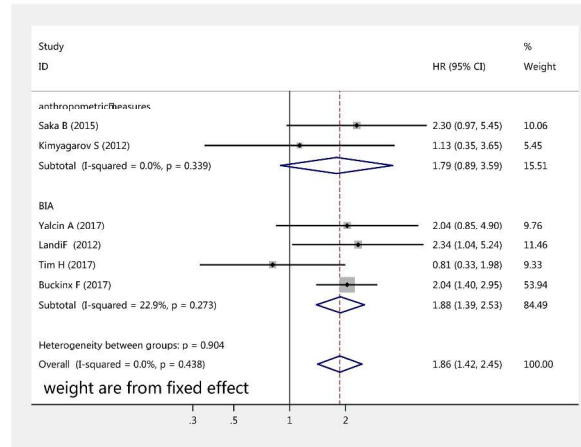


Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

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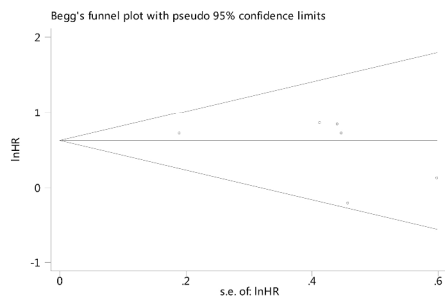


Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

Figure 5. Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

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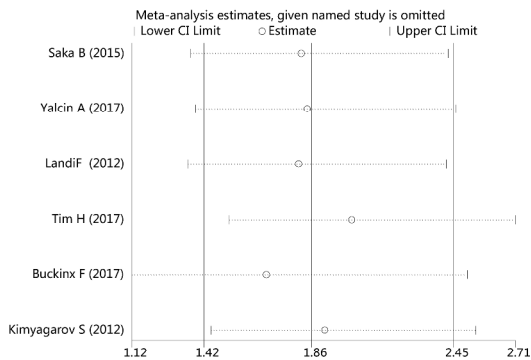


Figure.6 Sensitivity analysis of all studies.

Figure.6 Sensitivity analysis of all studies.

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11 #7: Search death*
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14 #10: Search (((("Survival"[Mesh]) OR survival*) OR death*) OR "Death"[Mesh]) OR mortality*) OR
15 "Mortality"[Mesh]
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17 OR "Mortality"[Mesh])) AND (("Sarcopenia"[Mesh]) OR sarcopenia*)
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31 #7: Search death*
32 #8: Search survival*
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MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	3
4	Type of exposure or intervention used	3
5	Type of study designs used	3
6	Study population	4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	None
8	Search strategy, including time period included in the synthesis and key words	4
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	4
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	4
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	7
26	Table giving descriptive information for each study included	7
27	Results of sensitivity testing (eg, subgroup analysis)	8
28	Indication of statistical uncertainty of findings	None

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	9
30	Justification for exclusion (eg, exclusion of non-English language citations)	9
31	Assessment of quality of included studies	None
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	11
34	Guidelines for future research	11
35	Disclosure of funding source	12

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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