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

Sarcopenia as a predictor of all-cause mortality amongolder nursing home 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 amongelderly 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 amongelderly 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 1year 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 amongolder 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 outcomesdue to cumulative deficits of multiple systems[1]. Particularly, nursing home residents are at high risk for Sarcopenia[2]. 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 hospitals[3]. Sarcopenia leads to worse outcome in elderly people including physical disability, fall, fractures, poor quality of life, mortality and hospitalization[4-6]. Among these, mortality might be considered the most importantoutcome 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, Liu[7]*et al* analyzed the sarcopenia and mortality with the conclusion that Sarcopenia is a predictor of all-cause mortality among

community-dwelling older people. However, there is no consistent conclusion regarding the relationship between sarcopenia and mortality among nursing home resident.It has been shown that the mortality rate in nursing home is approximately eightfold higher than that in the community, therefore, it is very important to confirm the risk factor for mortality among nursing home resident.

Several studies found that old people with sarcopenia were predictor of all-cause mortality among nursing home resident[8, 9]. However, some studies didn't find out any significant relationship between sarcopenia and all-causemortality[10-13]. Given the observed contradictory relationship between sarcopenia and all-cause mortality among nursing home resident in some studies, further studies are needed, However, no systematic review of meta-analysis studies on this topic have been conducted in the literature. Therefore, our study aims to identify and compare prospective cohort studies examining sarcopenia as a predictor of all-cause mortality among nursing home resident according to the PRISMA guidelines.

2. Materials and methods

This systematic review was undertaken and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14].

2.1. Search strategy and selection criteria

A systematic literature search were conducted in PubMed, EMBASE, and Cochrane CENTRAL Library Issue inNovember2017.The search strategy was tailored to according to each database. We used a combination of key words such as mortality(mortality*), OR death(death*), OR survival(survival*) and sarcopenia (sarcopenia*), as well as MeSH terms.Subject terms and truncation symbol were also used in our search strategy. We searched the potential gray studies through Google Scholar.Furthermore, a manual search was carried out on the references of included studies.

2.2. Study selection

These studiesidentified by our search strategy were reviewed by teamsof twoindependently blindedreviewers (Zhang XM and Wang CH)who evaluated each title and abstract. In case of disagreement on inclusion or exclusion of studies, this

issue was discussed and a third reviewer evaluated the study until consensus was reached by the reviewers.

2.3. Inclusion and exclusion criteria

The following eligibility and exclusion criteria were prespecified.Studies had to fulfill 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 among nursing home or nursing care. Exclusion criteria were as following:(1) Type of participant: community-dwelling older people (aged 65years and older) or hospitalized older people; (2) article type: only abstract, letters and laboratory research;review articles; (3) insufficient date;(4) other languages of studies, except English.

2.4. Data extraction

Two investigators(Zhang XM, Wang CH) independently abstracted the data from the selected studiesusing a standardized data-abstraction form. The following information were extracted from includedpapers: author, country,year of publication, demographic characteristics of participants (e.g., sample size, male proportion), measurement methods of sarcopenia, follow-up period,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)[15]: (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) contamination bias, and (6) other potential sources of bias. Articles were scored as follows:＞7 as high quality(NOS).

2.6. Statistical analysis

The STATA version 14.0(stata corp, College Station, TX, USA) was independently used for all analyses by two authors((Zhang XM, Dou QL). Hazard

ratios(HRs), odds ratio(OR) and their 95%CIs of mortality for sarcopenia compared with non-sarcopenia were extracted from studies for future meta-analysis. Subgroup analyses were conducted by sample size,follow-up period, if there was more than one study in the subgroup.The statistical heterogeneity among the included studies was examined with Cochran's Q statistic using chi-square and I^2 Statistics, and I^2 value of 25%,50% and75% represented the cut-off of low, moderate and high heterogeneity, respectively. if heterogeneity was found to be reasonably high between studies, the random effects model was used. Otherwise, the fixed effects model was used. Results were illustrated using forest plots.

3. Results

3.1. Search results

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

3.2 Included studies

Six prospective cohort studies were included in our meta-analysis with the total number of 1494 participants,Study characteristics ofincluded papers are displayed in table 1. There were 2 studies conducted in Turkey[16, 17], 1 studyin Italy[18-20],1 studyinAustralia [21],1 study in Belgium, 1 studyin Israel. All of the studies selected all-cause mortality as the clinical outcome, and used the sarcopenia criteria of EWGSOP. The EWGSOP defined sarcopenia in men as ALM adjusted for height squared $\leqslant$7.26 kg/m^2 OR$\leqslant$5.54kg/m^2 for women combined with low hand-grip strength (<30 kg) and low gait speed(<0.8 m/s),and/or low grip strength<30kg for men and<20 kg for women[22].The prevalenceof sarcopenia ranged from 32.8% to 73.3%.The largest study consisted of 662 men and women, and the smallest cohort only had 58 individuals. Follow-up periods were not longer varying from 6 mouths to 24 mouths, and the adjusted HR were displayed in four studies, and one was used OR,

the other one was RR.

3.3 Quality assessment

The methodological quality evaluation using NOS was shown in Table1. The score ranged from six to nine, the scores of five studies were more than seven.

3.4 Sarcopenia as a predictor of mortality

3.4.1Meta-analysis of studies

Sixstudies examined the association between sarcopenia and mortality among nursing home resident. The pooled HR values were calculated by fixed-effects models. As show in Figure2, The pooled hazard ratios (HRs) of all-cause mortality for sarcopenia versus the non-sarcopenia was 1.69(95%CI=1.24-2.30,P=0.001). No significant heterogeneity was observed across these studies((Q-value = 4.33, degree of freedom =5,I^2= 0%, p =0.503).

3.4.2Subgroup analysis

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

3.4.3 publication bias assessment

There was no significant publication among the studies using Begg's test:P=0.260.(Figure 5)

4. Discussion

In this meta-analysis, we found evidence suggesting the risk of all-cause mortality among nursing resident older people with Sarcopenia was higher than that among nursing resident older people without Sarcopenia. To the best of our

knowledge, this is the first meta-analysis to explore the relationship between Sarcopenia and all-cause mortality among nursing resident elderly people. Our study indicated assessing Sarcopenia is really important among the aged that living in nursing home or care.

Ping Liu[7] *et al*. implemented a systematic review and meta-analysis regarding the association of sarcopenia with mortality in 2016, published in 2017. However, this review including population were all involving community-dwelling older people. It is quite obvious that community-dwelling older people is totally different with the aged living in nursing home. Community-dwelling older people is relatively healthy, well-functioning individuals than elderly people living in nursing home. So far Shu-Fang Chang[23] and Beaudart[24] both performed a systematic review to evaluate the link between Sarcopenia and all-cause mortality, however there were some methodological shortcomings, such as various diagnostic criteria of Sarcopenia, crude ORs as effect, various population involving community-dwelling older people, hospitalized patients. Although subgroup of nursing home resident was analyze in Beaudart's study, there is only two research was assessed, which maybe underestimate or overestimated their result. There were six studies in our review, which only focus on the association of mortality and Sarcopenia in nursing home elderly people. We adopted the same diagnostic criteria of Sarcopenia(EWGSOP) and the Same type population (nursing home resident elderly people) to decreased clinical heterogeneity.

This meta-analysis of including six cohort studies, shows Sarcopenia is an important predictor of all-cause mortality among elderly nursing home resident. The pooled HR value of all-cause mortality was 1.69(95%CI=1.24-2.30, P=0.001, I^2 = 0%). The perfect I^2 suggesting no significant heterogeneity was showed across these researches. In addition our study pooled HR value is higher than Ping Liu(1.60 95%CI: 1.24–2.06), the primary reason was the different type of population. The aged living in nursing home usual had worse heath condition that may had more comorbidities, more disability and more geriatric syndromes, such as cognitive dysfunction and malnutrition[11, 25-27]. This comprehensive risk factor may aggravate the process of Sarcopenia.

The prevalence of Sarcopenia was 32.8-73.3% which is higher than other studies, the different was mainly due to the mean age, various population and different diagnostic tools, particularly the ways measure of muscle mass. Sarcopenia was associated with all-cause mortality in the size of sample 100 or more numbers group, but it was not significant in the size of less 100 group when subgroup was conducted according to size number in this systematic review.It was know that the larger the sample size, the more confident of the statistic. The subgroup of length of follow-up analysis was demonstrated that follow-up period 1year 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. The reason maybe,with the time of aging, Sarcopenia will aggravatingly impact to survival of patient , whichmay increase the rates of mortality.

The underlying mechanisms between sarcopenia and a higher risk of all-cause mortality did not have a conclusion, some aspects should be mentioned at least. Firstly Sarcopenia is linked to multifactor ranging to aging process[28], multiple Chronic health conditions, unhealthy lifestyle[29], hormomal factors[30], inflammation[31] and so on[32].In the 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 an increased poor adverse outcomes[33]. Secondly, according to the study of Fried[34]*et al.*, sarcopenia was an critical etiological role in the frailty process, which is related, through frailty, to pernicious consequences,For instance recurrent falls, bone fracture, disability, multiple emergency room visits and hospital admissions, and eventually death[35, 36]. For sarcopenia is a geriatric syndrome rather than a disease, the mechanism of Sarcopenia must be complex, which need more researches to explore.

Our meta-analysis review has multiple strengths and some limitation. One strength is 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. Another strength was the same unified diagnostic criteria of Sarcopenia(EWGSOP) and the same population(nursing home resident elderly

people) to reduce heterogeneity, and improve the research quality. There are some limitations in our studies. Firstly, the studies included in this analysis were insufficient and the size sample was relatively smaller. Secondly, 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. In addition, the follow-up was relatively short for the necessary latency, which maybe underestimate the results.

5. Conclusion

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

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8. Contributors

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

Conghua Wang was responsible for data extraction and for producing the initial draft of the manuscript.

Qingli Dou was responsible for data extraction.

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

Xiaohua Xiewas responsible for screening the papers.

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

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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Table1 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	12mouth	All-cause mortality	HR	Adjusted	8
Yalcin A	Turkey	2017	54.3%	141	79.17±7.99	EWGSOP	53.9	24mouth	All-cause mortality	HR	Adjusted	7
LandiF	Italy	2012	25%	122	84.1±4.8	EWGSOP	32.8	6mouth	All-cause mortality	HRs	Adjusted	9
Henwood T	Australia	2017	29.3%	58	85.7 ±8.2	EWGSOP	51.7	18mouth	All-cause mortality	RR	Adjusted	6
Buckinx F	Belgium	2017	27.5%	662	83.2 ±8.99	EWGSOP	36.2	12mouth	All-cause mortality	OR	Adjusted	7
Kimyagarov S	Israel	2012	41.2%	109	84.9±7.4	EWGSO	40.3	12mouth	All-cause mortality	HR	Adjusted	7

Figure 1.Search results and study selection.

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

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

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

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

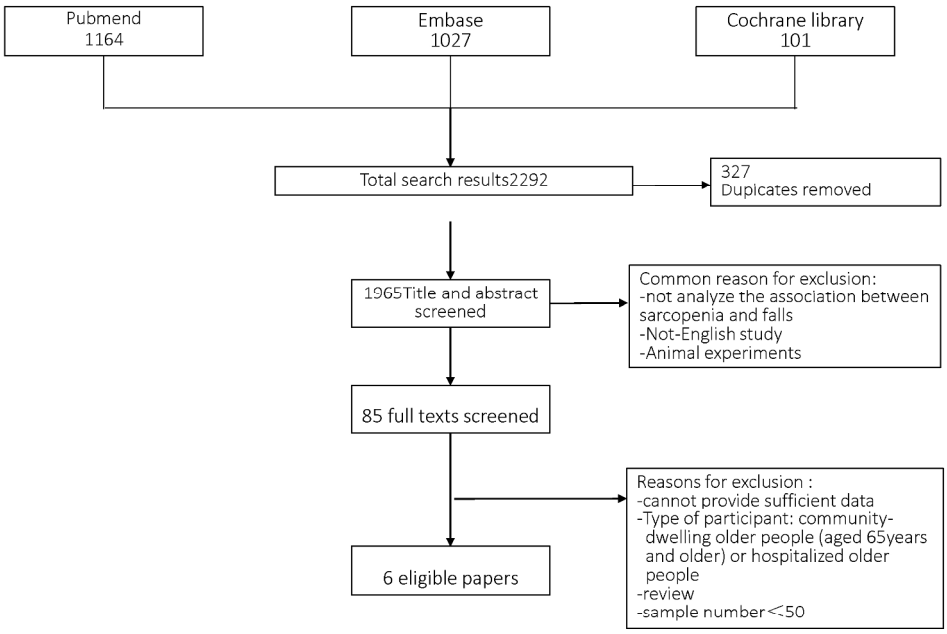

Figure 1.Search results and study selection

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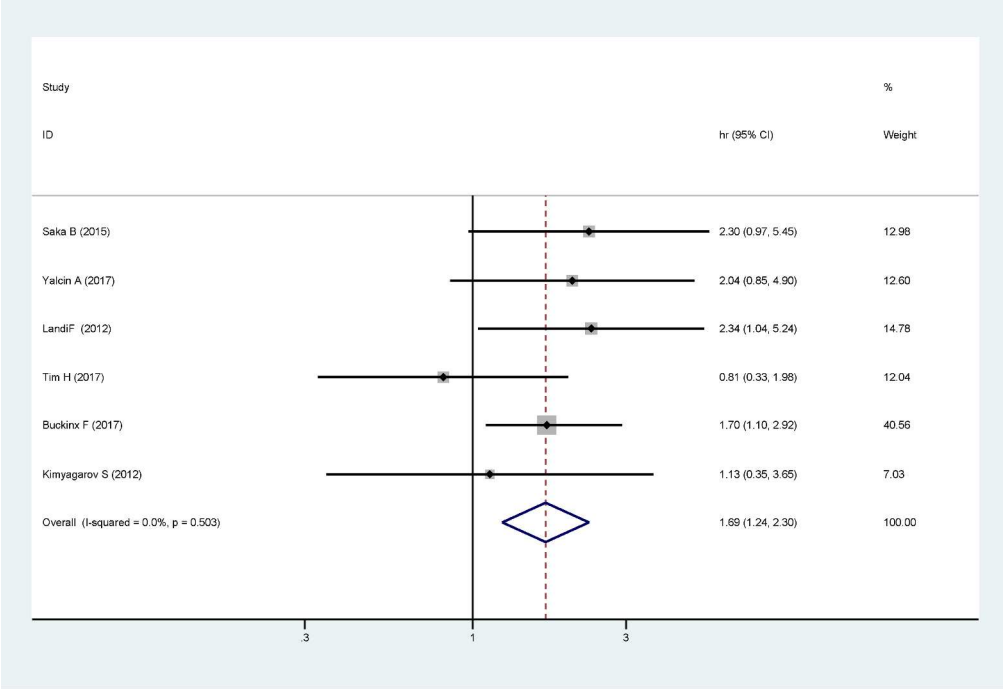

Figure 2. Meta-analysis of the association between Sarcopenia and mortality among older nursing home residents

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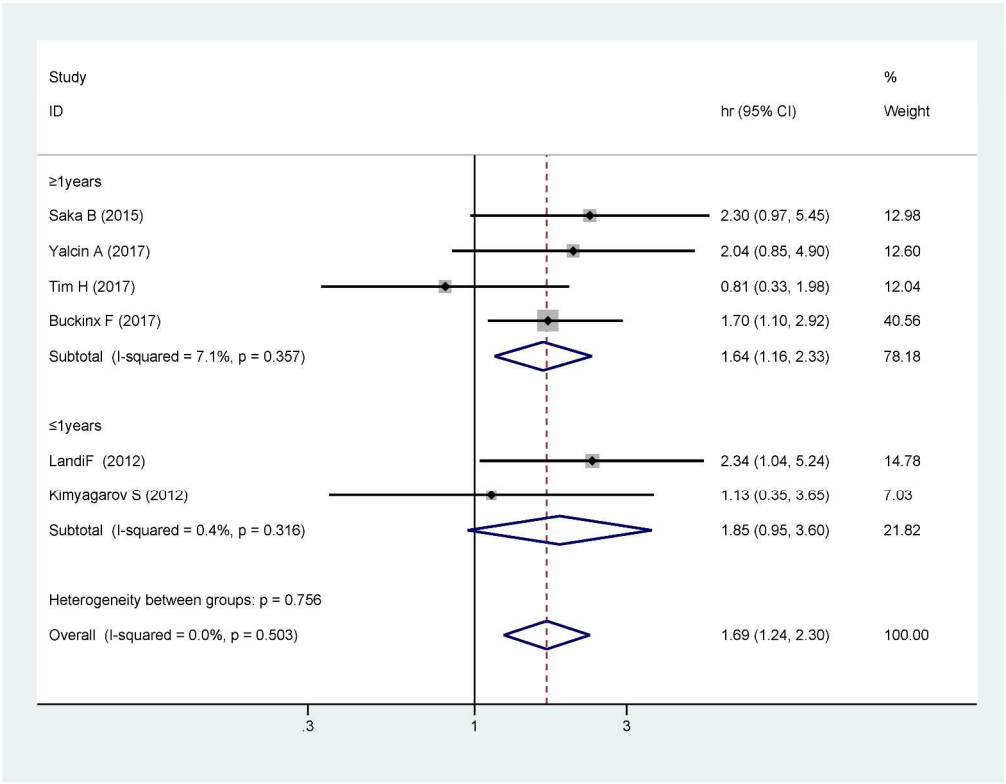

Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

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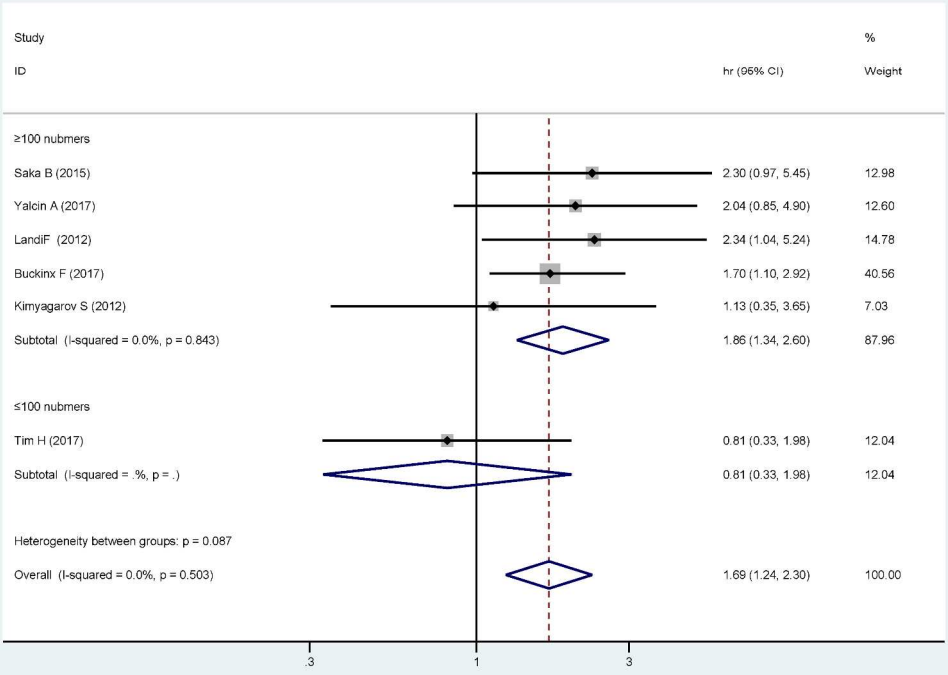

Figure 4. Subgroup analyses of the meta-analysis according to the sample size

275x207mm (300 x 300 DPI)

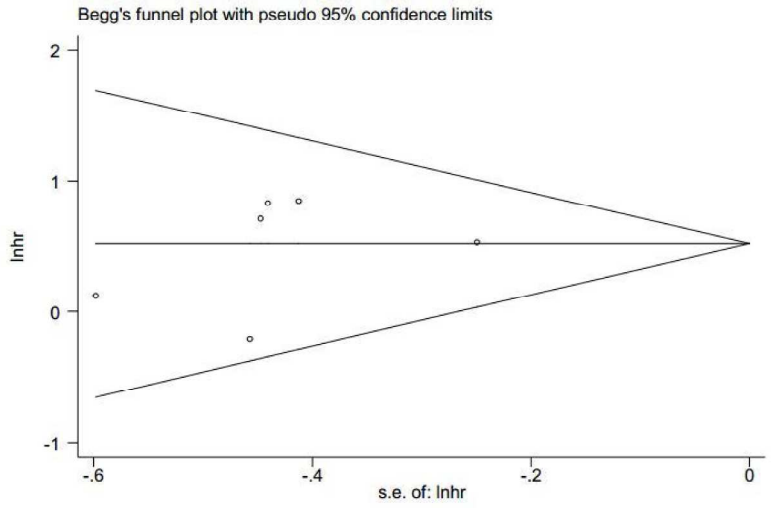

Figure 5.Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

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

318x206mm (300 x 300 DPI)

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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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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 systems[1]. Nursing home residents are at a particularly high risk for sarcopenia[2]. According to studies, the prevalence of sarcopenia was 1-29% for community-dwelling older adults, 14–85.4% in nursing homes[2-4] and 10-24.3% for those in hospitals[5]. Sarcopenia leads to a worse outcome in elderly people, including physical disability, falls, fractures, poor quality of life, mortality and hospitalisation[6-8]. 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, Liu[9] *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

regarding the relationship between sarcopenia and mortality among nursing home residents. It has been shown that the mortality rate in nursing homes[10] is approximately 2-fold higher than that in the community[11-13]; therefore, it is very important to confirm the risk factors for mortality among nursing home residents.

Several studies found that elderly people with sarcopenia were predictors of all-cause mortality among nursing home residents[14, 15]. However, some studies did not find any significant relationship between sarcopenia and all-cause mortality[16-19]. Given the observed contradictory relationship between sarcopenia and all-cause mortality among nursing home residents in some studies, further studies are needed. However, no systematic reviews of meta-analysis studies on this topic have been conducted in the literature. Therefore, our study aims to identify and compare prospective cohort studies examining sarcopenia as a predictor of all-cause mortality among nursing home residents according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Materials and methods

This meta-analysis was registered with the international prospective Register for Systemic Reviews (CRD42018081668) and conducted according to the PRISMA guidelines[20].

2.1. Search strategy and selection criteria

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

2.2. Study selection

These studies identified by our search strategy were reviewed by teams of two independently blinded reviewers (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. Patient and Public Involvement

Our meta-analysis was based on secondary data; therefore, the ethical approval, patient consent or Public Involvement was not necessary.

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

2.7. Statistical analysis

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

3. Results

3.1. Search results

The literature search strategy initially identified 2292 articles. After removal of duplicates, 1965 articles were screened for potential eligibility. A total of 85 publications remained for further consideration. Then we screened titles and abstracts and removed unrelated articles. Of these articles, 30 were removed because of not cohort studies (e.g., review articles, conference documents, cross-sectional study, case-control study), and six were removed because they had no clear definition of sarcopenia; moreover, 41 were removed on account of different

study population: community-dwelling older people, patients in hospital, and used the same cohorts (n = 2). These studies were screened according to the predefined inclusion and exclusion criteria for inclusion in the meta-analysis, resulting in a total of six eligible studies (Figure 1).

3.2 Included studies

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

3.3 Quality assessment

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

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 home residents without sarcopenia. To the best of our knowledge, this is the first meta-analysis to explore the relationship between sarcopenia and all-cause mortality among nursing home residents. Our study indicated assessing sarcopenia is really important among the elderly that live in nursing homes.

Ping Liu[9] *et al*. implemented a systematic review and meta-analysis regarding the association of sarcopenia with mortality in 2016, published in 2017. However, this review included a population entirely of community-dwelling older people. So far,

Shu-Fang Chang[31] and Beaudart[32] both performed a systematic review to evaluate the link between sarcopenia and all-cause mortality; however, there were some methodologic shortcomings, such as various diagnostic criteria of sarcopenia, crude ORs as effect, various population involving community-dwelling older people and hospitalised patients. Although a subgroup of nursing home residents was analysed in Beaudart's study, there is only two studies that was assessed, which maybe underestimated or overestimated their result. Our review included six studies which focus only on the association of mortality and sarcopenia in nursing home residents. We adopted the same diagnostic criteria of sarcopenia (EWGSOP) and the same type of population (nursing home residents) to decrease clinical heterogeneity.

This meta-analysis of six cohort studies shows sarcopenia is an important predictor of all-cause mortality among nursing home residents. The pooled HR value of all-cause mortality was 1.86 (95%CI=1.41-2.45, P=0.000, I^2 = 0%). The perfect I^2 suggesting no significant heterogeneity was shown across these research. In addition, our study's pooled HR value is higher than that of Ping Liu (1.60 95%CI: 1.24–2.06); the primary reason was the different type of population. Those living in a nursing home usually had worse heath conditions and more comorbidities, more disability and more geriatric syndromes, such as cognitive dysfunction and malnutrition[17, 33-35]. This comprehensive risk factor may aggravate the process of sarcopenia.

The prevalence of sarcopenia was 32.8-73.3%, which is higher than that in other studies. The difference was mainly due to the mean age, various population and different diagnostic tools, particularly the ways researchers measured muscle mass. Sarcopenia was associated with all-cause mortality when using BIA to diagnose muscle mass; whereas it was not associated when using anthropometric measures to diagnose muscle mass. According to the EWGSOP[1], BIA is the most common tool for diagnosing muscle mass; moreover, the test is inexpensive, easy to use, readily reproducible and appropriate for both ambulatory and bedridden patients, which may be considered a portable alternative toDXA (Dual Energy X-ray Absorptiometry) in nursing homes. However, the method of anthropometric measures was based on mid-upper-arm circumference and skin fold thickness[36]; therefore, age-related

changes in fat deposits and loss of skin elasticity contribute to errors of estimation in older nursing home residents, which are prone to produce errors[37]. Furthermore, anthropometric measures were not recommended for routine use in the diagnosis of sarcopenia. The subgroup of length of follow-up analysis demonstrated that 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=0.000); however, this was not found with the follow-up period of less than 1 year. The reason may be, with the time of aging, sarcopenia will aggravatingly impact patient survival, which may increase the mortality rates.

The underlying mechanisms between sarcopenia and a higher risk of all-cause mortality did not have a 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 mortality[38-40]. In addition, elderly people in nursing homes are at high risk of malnutrition[41], which aggravates low muscle mass, resulting in an increased mortality rate. Secondly, sarcopenia is linked to multiple factors ranging from aging process[42], multiple chronic health conditions, unhealthy lifestyle[43], hormonal factors[44], inflammation[45] and so on[46]. 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 outcomes[47]. Thirdly, according to the study of Fried[48] *et al.*, sarcopenia played a critical etiologic role in the frailty process, which is related, through frailty, to pernicious consequences—for instance, recurrent falls, bone fracture, disability, multiple emergency room visits and hospital admissions and eventually death[49, 50]. Moreover, sarcopenia is considered to increase the risk of falls among the elderly[51], and falls were the major causes of death in nursing home residents[52]. Sarcopenia is a geriatric syndrome rather than a disease; the mechanism of sarcopenia must be complex, which needs more research to explore.

Our meta-analysis review has multiple strengths and some limitations. One

strength is we used an extensive search process in electronic databases and assessed methodologic quality and tested the heterogeneity and publication bias among the included studies. Another strength was using the same unified diagnostic criteria of sarcopenia (EWGSOP) and the same population (nursing home residents) to reduce heterogeneity and improve the research quality. Our study had some limitations. Firstly, few included studies did not present the same confounding factors that were incorporated into the meta-analyses, which underestimated or overestimated our results. Especially, the Mini-Nutritional Assessment that was not included in two studies. However, malnutrition is very high among nursing home residents[41]. A study has shown that malnutrition is a risk for mortality among nursing home residents[17]. Another concern was that the cutoff for the muscle mass was different in some studies, which will cause the prevalence of Sarcopenia to be various, thus potentially influencing the result. The studies included in this analysis were insufficient, and the sample size was relatively small. Thirdly, the 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. In addition, the follow-up was relatively short for the necessary latency, which may underestimate the results.

5. Conclusion

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

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8. Contributors

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

Conghua Wang was responsible for data extraction and for producing the initial draft of the manuscript.

Qingli Dou was responsible for data extraction.

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

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

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

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Table1 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
LandiF	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

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	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
LandiF	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	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	1	1	1	1	1	1

	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

Figure 1. The flow diagram of studies selection.

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

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

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

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

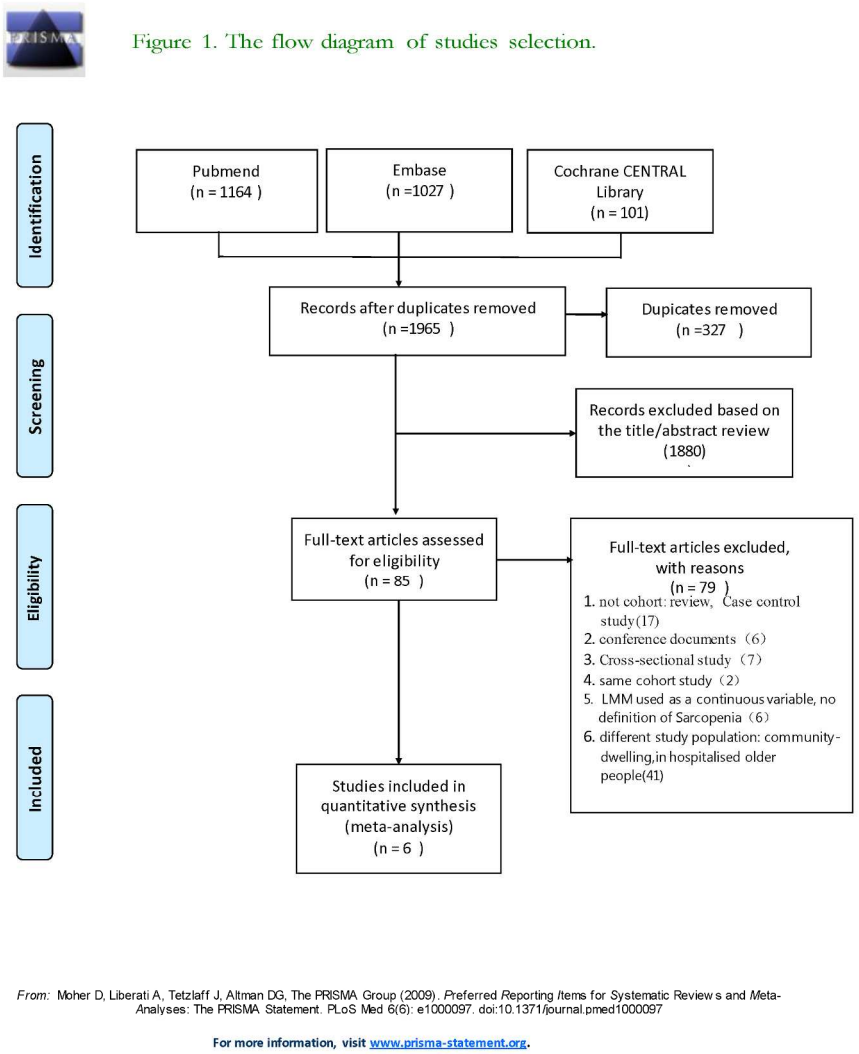

Figure 1. The flow diagram of studies selection.

215x279mm (300 x 300 DPI)

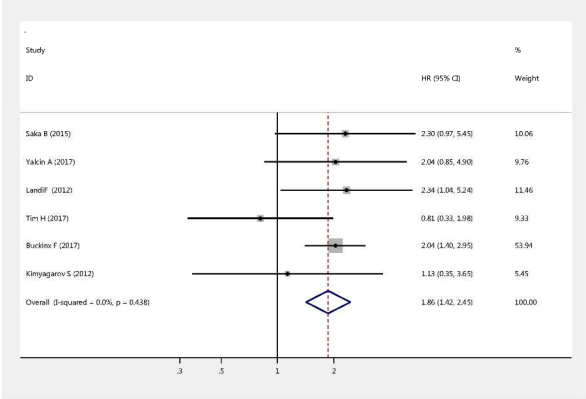

Figure 2. Meta-analysis of the association between sarcopenia and mortality among older nursing home residents.

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

210x297mm (300 x 300 DPI)

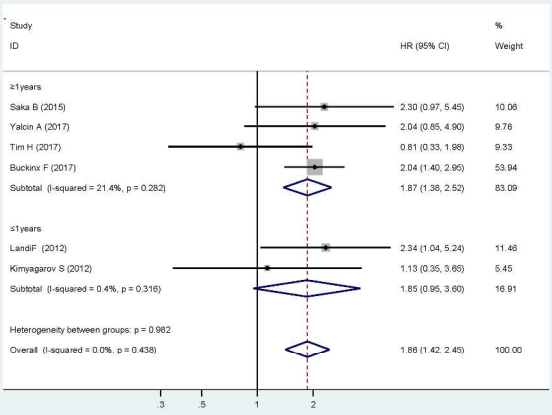

Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

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

210x297mm (300 x 300 DPI)

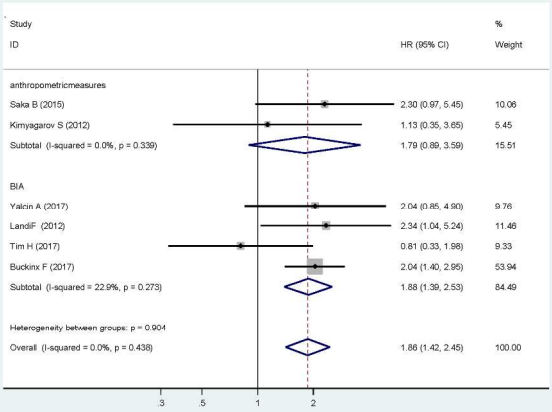

Figure 4: Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

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

210x297mm (300 x 300 DPI)

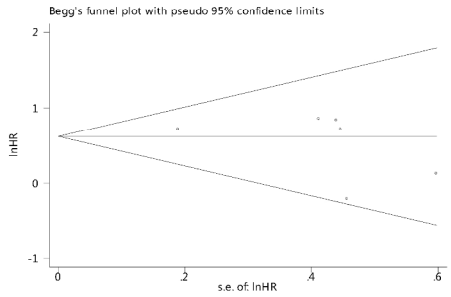

Figure 5.Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

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

210x297mm (300 x 300 DPI)

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
#3: #1OR #2
#4: Search MeSH descriptor: [mortality] explode all trees
#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

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

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

PRISMA 2009 Checklist

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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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Geriatric medicine, Nursing
Keywords:	Sarcopenia, All-cause mortality, Nursing Home, Meta-analysis, Sarcopenia; All-cause mortality; Nursing Home; Meta-analysis

Sarcopenia as a predictor of all-cause mortality among older nursing home 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: 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, 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=0.000); 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 systems[1]. Nursing home residents are at a particularly high risk for sarcopenia[2]. According to studies, the prevalence of sarcopenia was 1-29% for community-dwelling older adults, 14–85.4% in nursing homes[2-4] and 10-24.3% for those in hospitals[5]. Sarcopenia leads to a worse outcome in elderly people, including physical disability, falls, fractures, poor quality of life, mortality and hospitalisation[6-8]. 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, Liu[9] *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 regarding the relationship between sarcopenia and mortality among nursing home residents. It has been shown that the mortality rate in nursing homes[10] is approximately 2-fold higher than that in the community[11-13]; therefore, it is very important to confirm the risk factors for mortality among nursing home residents.

Several studies found that elderly people with sarcopenia were predictors of all-cause mortality among nursing home residents[14, 15]. However, some studies did not find any significant relationship between sarcopenia and all-cause mortality[16-19]. Given the observed contradictory relationship between sarcopenia and all-cause mortality among nursing home residents in some studies, further studies are needed. However, no systematic reviews of meta-analysis studies on this topic have been conducted in the literature. Therefore, our study aims to identify and compare prospective cohort studies examining sarcopenia as a predictor of all-cause mortality among nursing home residents according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Materials and methods

This meta-analysis was registered with the international prospective Register for Systemic Reviews (CRD42018081668) and conducted according to the PRISMA guidelines[20].

2.1. Search strategy and selection criteria

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

supplementary file.

2.2. Study selection

These studies identified by our search strategy were reviewed by teams of two independently blinded reviewers (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) contamination bias, and (6) other potential sources of bias. The total score of the scale is 9 points. When the total score is ≥ 5 points, it is considered a high-quality research.

2.6. Statistical analysis

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

2.7. Patient and Public Involvement

The patients or public were not involved in the study.

3. Results

3.1. Search results

The literature search strategy initially identified 2292 articles. After removal of duplicates, 1965 articles were screened for potential eligibility. A total of 85 publications remained for further consideration. Then we screened titles and abstracts and removed unrelated articles. Of these articles, 30 were removed because of non-

cohort studies (e.g., review articles, conference documents, cross-sectional study, case-control study), and six were removed because they had no clear definition of sarcopenia; moreover, 41 were removed on account of different study population: community-dwelling older people, patients in hospital, and used the same cohorts (n = 2). These studies were screened according to the predefined inclusion and exclusion criteria for inclusion in the meta-analysis, resulting in a total of six eligible studies (Figure 1).

3.2 Included studies

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

3.3 Quality assessment

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

home residents without sarcopenia. To the best of our knowledge, this is the first meta-analysis to explore the relationship between sarcopenia and all-cause mortality among nursing home residents. Our study indicated assessing sarcopenia is really important among the elderly that live in nursing homes.

Ping Liu[9] *et al*. implemented a systematic review and meta-analysis regarding the association of sarcopenia with mortality in 2016, published in 2017. However, this review included a population entirely of community-dwelling older people. So far, Shu-Fang Chang[31] and Beaudart[32] both performed a systematic review to evaluate the link between sarcopenia and all-cause mortality; however, there were some methodologic shortcomings, such as various diagnostic criteria of sarcopenia, crude ORs as effect, various population involving community-dwelling older people and hospitalised patients. Although a subgroup of nursing home residents was analysed in Beaudart's study, there is only two studies that was assessed, which maybe underestimated or overestimated their result. Our review included six studies which focus only on the association of mortality and sarcopenia in nursing home residents. the results were stable and reliable after we tested the heterogeneity and publication bias and performed sensitivity analysis among the included studies.

This meta-analysis of six cohort studies shows sarcopenia is an important predictor of all-cause mortality among nursing home residents. The pooled HR value of all-cause mortality was 1.86 (95%CI=1.41-2.45, P=0.000, I^2 = 0%). The perfect I^2 suggesting no significant heterogeneity was shown across these research. In addition, our study's pooled HR value is higher than that of Ping Liu (1.60 95%CI: 1.24–2.06); the primary reason was the different type of population. Those living in a nursing home usually had worse heath conditions and more comorbidities, more disability and more geriatric syndromes, such as cognitive dysfunction and malnutrition[17, 33-35]. This comprehensive risk factor may aggravate the process of sarcopenia.

The prevalence of sarcopenia was 32.8-73.3%, which is higher than that in other studies. The difference was mainly due to the mean age, various population and different diagnostic tools, particularly the ways researchers measured muscle mass.

Sarcopenia was associated with all-cause mortality when using BIA to diagnose muscle mass; whereas it was not associated when using anthropometric measures to diagnose muscle mass. According to the EWGSOP[1], BIA is the most common tool for diagnosing muscle mass; moreover, the test is inexpensive, easy to use, readily reproducible and appropriate for both ambulatory and bedridden patients, which may be considered a portable alternative to DXA (Dual Energy X-ray Absorptiometry) in nursing homes. However, the method of anthropometric measures was based on mid-upper-arm circumference and skin fold thickness[36]; therefore, age-related changes in fat deposits and loss of skin elasticity contribute to errors of estimation in older nursing home residents, which are prone to produce errors[37]. Furthermore, anthropometric measures were not recommended for routine use in the diagnosis of sarcopenia. The subgroup of length of follow-up analysis demonstrated that follow-up period of 1 year or more was associated with all-cause mortality (pooled HR=1.87,95%CI 1.38-2.52, p=0.000); however, it was not found with the follow-up period of less than 1 year. The power for the short term analyses was too small to have a significant result. Therefore, more perspective cohort studies about this issue must be conducted in the future.

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 mortality[38-40]. In addition, elderly people in nursing homes are at high risk of malnutrition[41], which aggravates low muscle mass, resulting in an increased mortality rate. Secondly, sarcopenia is linked to multiple factors ranging from aging process[42], multiple chronic health conditions, unhealthy lifestyle[43], hormonal factors[44], inflammation[45] and so on[46]. 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

outcomes[47]. Thirdly, according to the study of Fried[48] *et al.*, sarcopenia played a critical etiologic role in the frailty process, which is related, through frailty, to pernicious consequences—for instance, recurrent falls, bone fracture, disability, multiple emergency room visits and hospital admissions and eventually death[49, 50]. Moreover, sarcopenia is considered to increase the risk of falls among the elderly[51], and falls were the major causes of death in nursing home residents[52]. Sarcopenia is a geriatric syndrome rather than a disease; the mechanism of sarcopenia must be complex, which needs more research to explore.

Our meta-analysis review has multiple strengths and some limitations. One strength was that we used an extensive search process in electronic databases and assessed methodologic quality and tested the heterogeneity and publication bias among the included studies. Another strength was that the included original studies were all of prospective design, which minimized the possibility of recall bias and selection bias. However, our study also has some limitations. Firstly, two included studies did not directly report the HR in the sarcopenia group versus the non-sarcopenia group, but used an approximation of OR to RR, and from RR to HR in the sarcopenia group, which might not show an accurate HR value. Therefore, this approach may lead to method heterogeneity. Another concern was that the cut-off for the muscle mass was different in some studies, which will cause the prevalence of Sarcopenia to be various, thus potentially influencing the result. Thirdly, the number of included studies in this analysis was insufficient, and the sample size was relatively small. Fourthly, we ignored the different adjusted confounding factors of the derived HR from different studies. Fifthly, the 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. In addition, the follow-up was relatively short for the necessary latency, which may underestimate the results.

5. Conclusion

This study provides evidence that sarcopenia is a significant predictor of all-cause mortality among nursing home residents based on the comprehensive systematic

review and meta-analysis. Further studies are needed to provide evidence for specific interventions to prevent and treat sarcopenia, which can reduce mortality in people living in a nursing home.

6. Acknowledgements

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8. Contributors

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

Conghua Wang was responsible for data extraction and for producing the initial draft of the manuscript.

Qingli Dou was responsible for data extraction.

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

Xiaohua Xiewas responsible for screening the papers.

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

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. 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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Table1 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
LandiF	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

											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

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

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

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	Handgrip strength	None	SPPB: Short Physical Performance Battery	≤0.8m/s	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	NIH-sponsored workshop	anthropometric measures	SMM index: (males) < 10.5 kg/m2 (females)< 8.5 kg/m2	manual muscle testing	MMT* score<106	None	None	19

LandiF	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

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

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

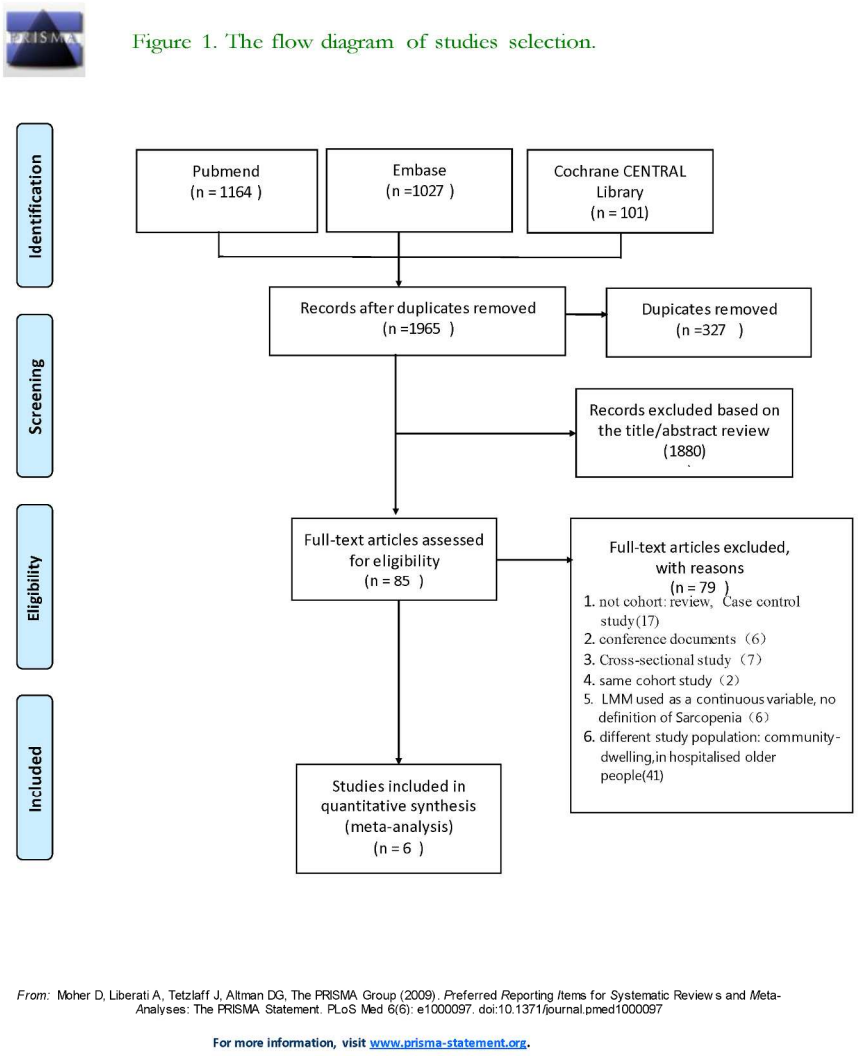

Figure 1. The flow diagram of studies selection.

215x279mm (300 x 300 DPI)

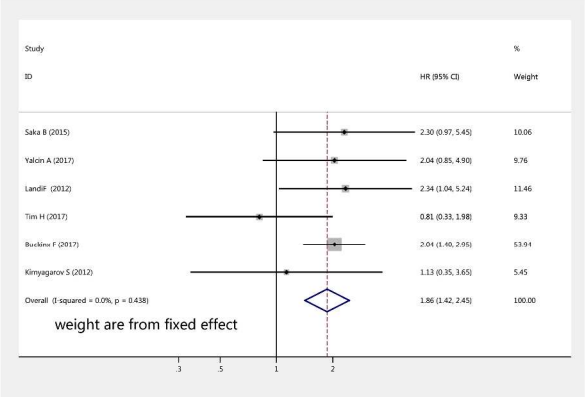

Figure 2. Meta-analysis of the association between Sarcopenia and mortality

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

297x420mm (300 x 300 DPI)

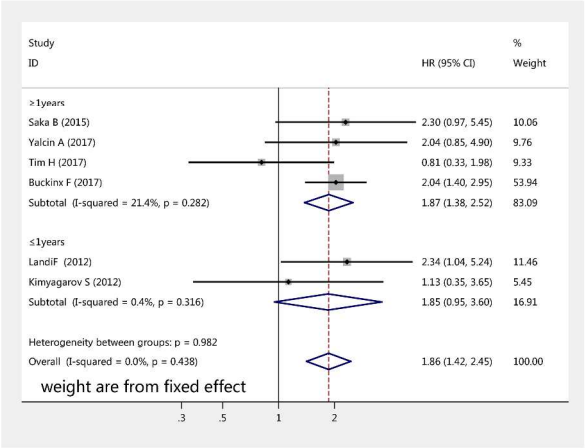

Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

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

297x420mm (300 x 300 DPI)

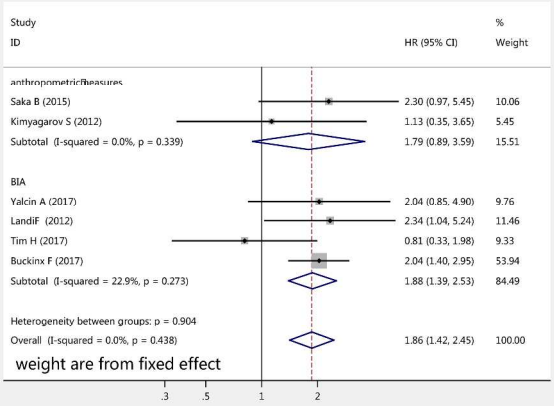

Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

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

297x420mm (300 x 300 DPI)

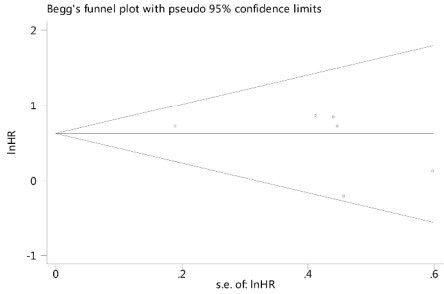

Figure 5.Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

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

297x420mm (300 x 300 DPI)

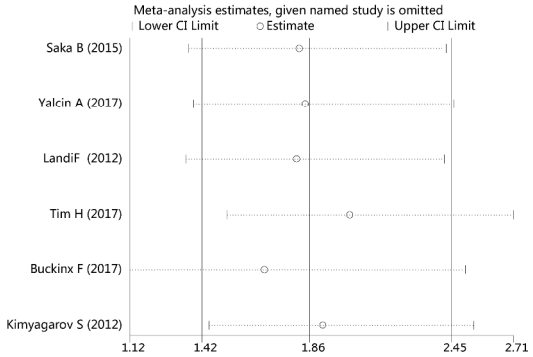

Figure.6 Sensitivity analysis of all studies.

Figure.6 Sensitivity analysis of all studies.

297x420mm (300 x 300 DPI)

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
#3: #1OR #2
#4: Search MeSH descriptor: [mortality] explode all trees
#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

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

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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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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 systems[1]. Nursing home residents are at a particularly high risk for sarcopenia[2]. According to studies, the prevalence of sarcopenia was 1-29% for community-dwelling older adults, 14–85.4% in nursing homes[2-4] and 10-24.3% for those in hospitals[5]. Sarcopenia leads to a worse outcome in elderly people, including physical disability, falls, fractures, poor quality of life, mortality and hospitalisation[6-8]. 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, Liu[9] *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 regarding the relationship between sarcopenia and mortality among nursing home residents. It has been shown that the mortality rate in nursing homes[10] is approximately 2-fold higher than that in the community[11-13]; therefore, it is very important to confirm the risk factors for mortality among nursing home residents.

Several studies found that elderly people with sarcopenia were predictors of all-cause mortality among nursing home residents[14, 15]. However, some studies did not find any significant relationship between sarcopenia and all-cause mortality[16-19]. Given the observed contradictory relationship between sarcopenia and all-cause mortality among nursing home residents in some studies, further studies are needed. However, no systematic reviews of meta-analysis studies on this topic have been conducted in the literature. Therefore, our study aims to identify and compare prospective cohort studies examining sarcopenia as a predictor of all-cause mortality among nursing home residents according to the MOOSE guidelines

2. Materials and methods

This meta-analysis was registered with the international prospective Register for Systemic Reviews (CRD42018081668) and conducted according to the MOOSE guidelines[20].

2.1. Search strategy and selection criteria

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

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)

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

2.6. Statistical analysis

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

2.7. Patient and Public Involvement

The patients or public were not involved in the study.

3. Results

3.1. Search results

The literature search strategy initially identified 2,292 articles. After removal of duplicates, 1,965 articles were screened for potential eligibility. A total of 85 publications remained for further consideration. Then we screened titles and abstracts and removed unrelated articles. Of these articles, 30 were removed because of non-cohort studies (e.g., review articles, conference documents, cross-sectional study,

case-control study), and six were removed because they had no clear definition of sarcopenia; moreover, 41 were removed on account of different study population: community-dwelling older people, patients in hospital, and used the same cohorts (n = 2). These studies were screened according to the predefined inclusion and exclusion criteria for inclusion in the meta-analysis, resulting in a total of six eligible studies (Figure 1).

3.2 Included studies

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

3.3 Quality assessment

The methodological quality evaluation using NOS of all items is shown in Table 3. The score of each study ranged from six to nine. The scores of five studies were more 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 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 pooing 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

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 home residents without sarcopenia. To the best of our knowledge, this is the first meta-analysis to explore the relationship between sarcopenia and all-cause mortality among nursing home residents. Our study indicated assessing sarcopenia is really important among the elderly that live in nursing homes.

Ping Liu[9] *et al*. implemented a systematic review and meta-analysis regarding the association of sarcopenia with mortality in 2016, published in 2017. However, this review included a population entirely of community-dwelling older people. So far, Shu-Fang Chang[32] and Beaudart[33] both performed a systematic review to evaluate the link between sarcopenia and all-cause mortality; however, there were some methodological shortcomings, such as various diagnostic criteria of sarcopenia, crude ORs as effect, various population involving community-dwelling older people and hospitalised patients. Although a subgroup of nursing home residents was analysed in Beaudart's study, there is only two studies that was assessed, which maybe underestimated or overestimated their result. Our review included six studies which focus only on the association of mortality and sarcopenia in nursing home residents. The results were stable and reliable after we tested the heterogeneity and publication bias and performed sensitivity analysis among the included studies.

This meta-analysis of six cohort studies shows sarcopenia is an important predictor of all-cause mortality among nursing home residents. The pooled HR value of all-cause mortality was 1.86 (95%CI=1.41-2.45, $p<0.001$, $I^2 = 0\%$). The small I^2 suggesting no significant heterogeneity was shown across these studies. In addition, our study's pooled HR value is higher than that of Ping Liu[9] (1.60 95%CI: 1.24–2.06); the primary reason was the different type of population. Those living in a nursing home usually had worse heath conditions and more comorbidities, more disability and more geriatric syndromes, such as cognitive dysfunction and malnutrition[17, 34-36]. This comprehensive risk factor may aggravate the process of sarcopenia.

In our present study, the prevalence of sarcopenia varied from 32.8-73.3%. The

difference was mainly due to the mean age, various population and different diagnostic tools, particularly the ways that researchers measured muscle mass. A previous study showed that sarcopenia was associated with mortality when BIA was used to diagnose muscle mass[37]. In this present study, we confirmed that sarcopenia was associated with all-cause mortality using BIA to diagnose muscle mass; however, the association was not found when using anthropometric measures. According to the EWGSOP[1], BIA is the most common tool for diagnosing muscle mass; moreover, the test is inexpensive, easy to use, readily reproducible and appropriate for both ambulatory and bedridden patients, which may be considered a portable alternative to DXA (Dual Energy X-ray Absorptiometry) in nursing homes. However, the method of anthropometric measures was based on mid-upper-arm circumference and skin fold thickness[38]; therefore, age-related changes in fat deposits and loss of skin elasticity contribute to errors of estimation in older nursing home residents, which are prone to produce errors[39]. Furthermore, anthropometric measures were not recommended for routine use in the diagnosis of sarcopenia.

It has been demonstrated that length follow-up could influence the association between sarcopenia and mortality[9]. Our study showed that the subgroup of length of follow-up analysis demonstrated that follow-up period of 1 year or more was associated with all-cause mortality (pooled HR=1.87,95%CI 1.38-2.52, p<0.001); however, it was not found with the follow-up period of less than 1 year (pooled HR=1.85, 95%CI 0.95-3.60, p=0.070). It is noticed that there were only 231 cases in the two studies with the follow-up period of less than 1 year and it is likely that the numbers of studies and included cases for short term analysis were too small to have a significant result. Therefore, more perspective cohort studies about this issue must be conducted in the future.

The underlying mechanisms between sarcopenia and a higher risk of all-cause mortality were unable to draw a 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 mortality[40-42]. In addition, elderly people in nursing homes are at high risk of malnutrition[43], which aggravates low muscle mass, resulting in an increased mortality rate. Secondly, sarcopenia is linked to multiple factors ranging from aging process[44], multiple chronic health conditions, unhealthy lifestyle[45], hormonal factors[46], inflammation[47] and so on[48]. Meanwhile, the above factors are considered to be linked with 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 outcomes[49]. Thirdly, according to the study of Fried[50] *et al.*, sarcopenia played a critical etiologic role in the frailty process, which is related, through frailty, to pernicious consequences, for instance, recurrent falls, bone fracture, disability, multiple emergency room visits and hospital admissions and eventually death[51, 52]. Moreover, sarcopenia is considered to increase the risk of falls among the elderly[53], and falls were the major causes of death in nursing home residents[54]. Sarcopenia is a geriatric syndrome rather than a disease; the mechanism of sarcopenia is very complex, which needs more research to explore.

Our meta-analysis review has multiple strengths and some limitations. One strength was that we used an extensive search process in electronic databases and assessed methodological quality and tested the heterogeneity and publication bias among the included studies. Another strength was that the included original studies were all of prospective design, which minimized the possibility of recall bias and selection bias. However, our study also has some limitations. Firstly, two included studies did not directly report the HR in the sarcopenia group versus the non-sarcopenia group, but used an approximation of OR to RR, and from RR to HR in the sarcopenia group, which might not show an accurate HR value. Therefore, this approach may lead to method heterogeneity. Another concern was that the cut-off for the muscle mass was different in some studies, which caused the prevalence of Sarcopenia to be various, thus potentially influenced the result. Thirdly, the number of included studies in this analysis was insufficient, and the sample size was relatively small. Fourthly, we

ignored the different adjusted confounding factors of the derived HR from different studies. Fifthly, the language of studies was limited to English, and consequently some data from important studies published in other languages have been ignored, which may result in potential language bias. In addition, the follow-up was relatively short for the necessary latency, which may underestimate the results.

5. Conclusion

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

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8. Contributors

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

Conghua Wang was responsible for data extraction and for producing the initial draft of the manuscript.

Qingli Dou was responsible for data extraction.

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

Xiao Hua Xie was responsible for screening the papers.

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

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. 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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Table1 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
LandiF	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

											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

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

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

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	Handgrip strength	None	SPPB: Short Physical Performance Battery	≤0.8m/s	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	NIH-sponsored workshop	anthropometric measures	SMM index: (males) < 10.5 kg/m2 (females)< 8.5 kg/m2	manual muscle testing	MMT* score<106	None	None	19

LandiF	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

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

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

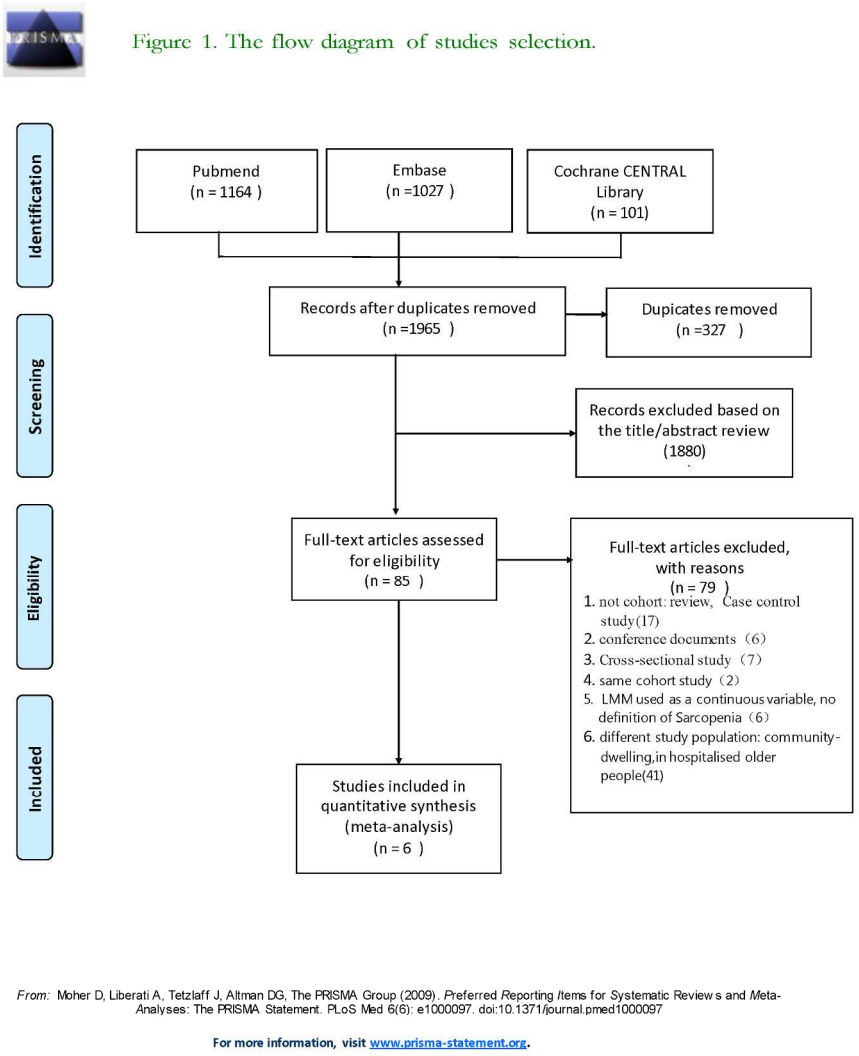

Figure 1. The flow diagram of studies selection.

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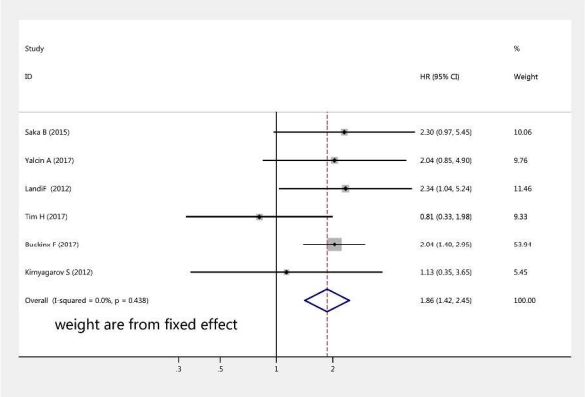

Figure 2. Meta-analysis of the association between Sarcopenia and mortality

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

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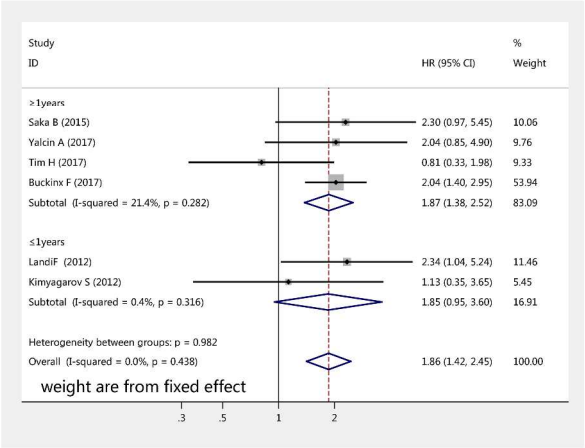

Figure 3. Subgroup analyses of the meta-analysis according to length of follow-up

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

297x420mm (300 x 300 DPI)

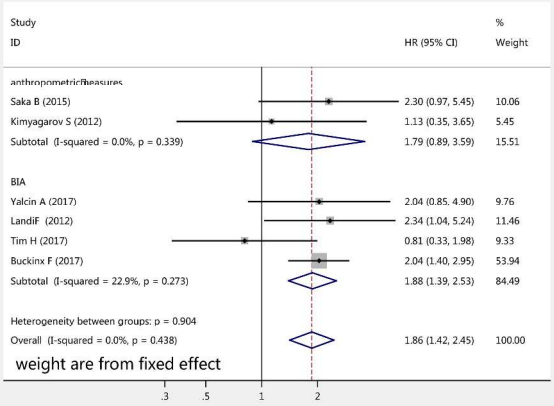

Figure 4. Subgroup analyses of the meta-analysis according to different diagnosis tools for muscle mass.

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

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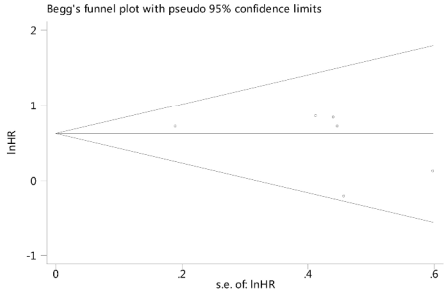

Figure 5.Funnel plot of sarcopenia and all-cause mortality among older nursing home residents

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

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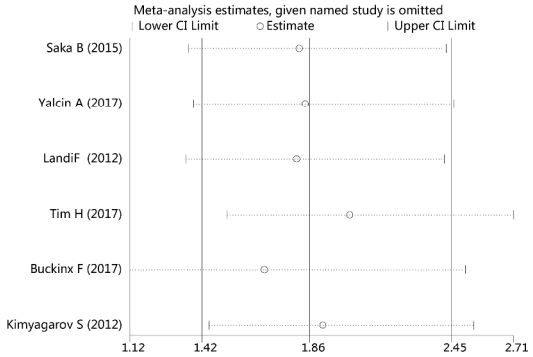

Figure.6 Sensitivity analysis of all studies.

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297x420mm (300 x 300 DPI)

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
#3: #1OR #2
#4: Search MeSH descriptor: [mortality] explode all trees
#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

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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