





BMJ Open Is sarcopenia associated with anxiety symptoms and disorders? A systematic review and meta-analysis protocol

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ABSTRACT

Introduction Sarcopenia is a skeletal muscle disorder characterised by a progressive decline in muscle mass and function (strength and performance). Sarcopenia is associated with numerous adverse health outcomes and has recently been linked to neurological and psychiatric disorders, including dementia and depression. Whether sarcopenia is related to other common psychiatric illnesses, such as anxiety, is unclear. We aim to systematically identify and review the extant literature regarding the association between sarcopenia and anxiety symptomatology and/or disorders (anxiety) in adults.

Methods and analysis We will conduct a systematic search across four online databases (CINAHL, Embase, MEDLINE Complete and PsycINFO) from inception to September 2021. Two reviewers will independently confirm study selection and assess methodological quality of included studies. If possible, a meta-analysis will be performed to determine pooled OR for the relationship between sarcopenia and anxiety. If meta-analysis is not possible due to methodological heterogeneity a 'best evidence synthesis' will be performed.

Ethics and dissemination This review will use published data only, thus, ethical approval will not be required. Findings will be published in a peer-reviewed journal and presented at conferences.

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INTRODUCTION

Sarcopenia is a skeletal muscle disorder characterised by a progressive decline in muscle mass and function (strength and performance).¹ It is primarily age related and affects approximately 10% of adults aged ≥ 60 years.² Sarcopenia is associated with numerous adverse health outcomes including functional decline,³ falls,^{3–5} fractures,⁴ hospitalisation⁶ and mortality.^{3–7} An emerging body of evidence suggests sarcopenia is also associated with neurological and psychiatric disorders such as cognitive impairment,^{8–9} dementia¹⁰ and depression.^{11–13}

Anxiety disorders are among the most common psychiatric disorders worldwide.¹⁴ In Australia, reported lifetime prevalence of anxiety disorders is 13.5% for women¹⁵

Strengths and limitations of this study

- This study will be the first to systematically assess the literature on the association between sarcopenia and anxiety.
- Two reviewers will independently confirm study selection and assess methodological quality of included studies.
- Meta-analysis is contingent on heterogeneity of available evidence.
- Non-English studies will not be considered, potentially introducing language bias.

and 7.2% for men.¹⁶ The economic burden associated with anxiety is substantial to both individuals and society. Total annual health-care costs associated with anxiety disorders in 2007 was an estimated \$A376 million, which consisted of \$A77.9 million to individuals.¹⁷ Co-occurrence of physical disorders, including musculoskeletal diseases, is common among individuals with anxiety.^{18–20} However, whether sarcopenia is related to anxiety is unclear.

There are a number of potential mechanisms linking sarcopenia and psychiatric disorders.²¹ Skeletal muscle contractions produce neurotrophic factors, such as brain derived neurotrophic factor, which is known to play a role in mood disorders and has also been implicated in anxiety disorders.²² Chronic inflammation is known to play a crucial role in the progression of sarcopenia^{23–24} as well as influencing the expression and evolution of anxiety disorders.²⁵ Furthermore, sarcopenia and anxiety share a number of common lifestyle risk factors including physical inactivity, poor nutrition and smoking.²¹

Data from recent observational studies investigating associations between sarcopenia and anxiety appear inconsistent. Some studies report no association between muscle function and anxiety,^{26–27} whereas other studies have reported associations between

low muscle strength and the onset and persistence of anxiety.^{28 29} Evidence regarding other putative components of sarcopenia, such as muscle mass, also appear conflicting. A recent cross-sectional analysis of 113 haemodialysis patients reported an inverse association between loss of muscle mass and high anxiety distress scores.³⁰ Conversely, a study of 237 patients with cancer found no association between muscle mass and anxiety scores.³¹ To date, no attempt has been made to synthesise evidence regarding associations between sarcopenia and anxiety. To address this gap in the literature, we will systematically identify and review the extant literature regarding the association between sarcopenia and anxiety in adults.

Objectives

This systematic review will:

1. Identify published studies that investigate the association between sarcopenia and anxiety.
2. Evaluate the methodological quality of included studies.
3. Collate the evidence and provide a comprehensive synthesis of the findings.

METHODS AND ANALYSIS

This protocol has been developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols guidelines.³² The methods for this systematic review have been developed according to recommendations from the PRISMA statement.³³

Inclusion and exclusion criteria

Studies will be included if they meet the following criteria:

Study design

Case-control, cross-sectional, cohort designs and clinical trials (baseline data) will be included. Case reports, grey literature and animal studies will be excluded.

Participants

Studies involving adults aged 18 years or older of any nationality. Community-dwelling, institutionalised and clinical samples will all be eligible for inclusion.

Sarcopenia

Studies that include a measure of sarcopenia as defined by a professional group, such as: the European Working Group on Sarcopenia in Older Persons^{1 34}; the Asian Working Group for Sarcopenia^{35 36}; the Foundation for the National Institutes of Health³⁷; Special Interest Group³⁸; the Society on Sarcopenia, Cachexia and Wasting Disorders³⁹; International Working Group on Sarcopenia⁴⁰ and Sarcopenia Definition and Outcomes Consortium.⁴¹ Full definitions proposed by these professional groups are presented in [table 1](#). Given the current absence of a universal definition, studies examining putative components of sarcopenia (muscle mass and muscle function) will also be included.

Anxiety

Symptoms of anxiety as measured by a validated symptom scale or diagnoses of anxiety-related disorders based on the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases classification systems. Studies that focus on anxiety related to fear of falling, pain and appearance will be excluded. Studies that assess comorbid depression or general mental health will be excluded.

Search strategy

We will perform an electronic search across four databases: CINAHL, Embase, MEDLINE Complete and PsycINFO. The search strategy was developed alongside a medical librarian using a combination of free-text terms and controlled vocabulary terms (CINAHL SH/Emtree/MeSH/APA Thesaurus). The search strategy was designed to be broad and inclusive of all conceptualisations of sarcopenia and its putative components. Keywords were drawn from relevant literature and further refined using a 'gold set' of articles. There will be no restrictions on publication date, studies will be included from inception to September 2021. An illustrative example of the search strategy is presented in [table 2](#). Full search strategy adapted for each database is available in online supplemental material. For completeness, we will handsearch the reference lists of included studies and other relevant articles to identify further potentially relevant citations.

Data management and extraction

We will download the references identified in our electronic searches into EndNote V.X9 reference management software (Thomas Reuters, New York, USA) where duplicates will be manually removed. The remaining references will be exported into Covidence,⁴² an online software used for systematic review data management. Titles and abstracts of records identified in the search will be independently screened for eligibility by two reviewers using a prepiloted screening/selection tool that incorporates the predetermined inclusion criteria described in this protocol. The screening/selection tool will be piloted on approximately 30 titles and abstracts. If there are any conflicts between reviewers' decisions during pilot testing, the review team will meet to discuss and refine the screening/selection tool. Full-text articles will be retrieved for studies that satisfy the eligibility criteria in title and abstract screening. Full-text articles will be independently assessed by two reviewers using the screening/selection tool with disagreements resolved by discussion until consensus is reached. A third reviewer will be consulted where necessary to reach consensus. A PRISMA flow diagram will be used to document the screening and selection process including reasons for exclusion in line with the predetermined eligibility criteria.³³

A custom data extraction form will be used to collate information from included studies. The key information to be extracted will include but may not be limited to: (1) study name; (2) country and year; (3) population

Table 1 Sarcopenia definitions and proposed cut-offs

Professional group	Sarcopenia definition
Asian Working Group for Sarcopenia (AWGS) (2014) ³⁵	<p>Low muscle mass plus low muscle strength and/or low physical performance.</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Handgrip strength <26 kg for males, <18 kg for females ▶ Gait speed <0.8 m/s ▶ Height adjusted muscle mass using dual-energy X-ray absorptiometry <7.0 kg/m² for males, <5.4 kg/m² for females ▶ Height adjusted muscle mass using bioimpedance <7.0 kg/m² for males, <5.7 kg/m² for females
AWGS (2019) ³⁶	<p>Low muscle mass plus low muscle strength and/or low physical performance.</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Handgrip strength <28 kg for males, <18 kg for females ▶ 6 m walk <1.0 m/s ▶ Short Physical Performance Battery score ≤9 ▶ 5-time chair stand test ≥12 s ▶ AWGS 2019 retains the original cut-offs for height-adjusted muscle mass
European Working Group on Sarcopenia in Older Persons (EWGSOP) (2010) ³⁴	<p>Presence of both low muscle mass and low muscle function (strength or performance).</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Gait speed ≤0.8 m/s ▶ Offers examples from literature of various cut-off points for muscle mass and handgrip strength
EWGSOP2 (2019) ¹	<p>Low muscle strength key characteristic, low muscle quantity and quality to confirm diagnosis. Physical performance as indicator of severity.</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Grip strength <27 kg for males, <16 kg for females ▶ Gait speed ≤0.8 m/s ▶ Short Physical Performance Battery score ≤8 ▶ Timed up and go ≥20 s ▶ Chair stand >15 s for five rises ▶ 400 m walk test non-completion or ≥6 min for completion
Foundation for the National Institutes of Health (2014) ³⁷	<p>Low muscle mass and weakness.</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Appendicular lean mass adjusted for BMI <0.789 for males, <0.512 for females ▶ Gait speed <0.8 m/s ▶ Grip strength <26 kg for males, <16 kg for females
International Working Group on Sarcopenia (2011) ⁴⁰	<p>Loss of skeletal muscle mass and function.</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Gait speed less than 1 m/s ▶ Appendicular mass relative to height ≤7.23 kg/m² for males, ≤5.67 kg/m² for females
Sarcopenia Definition and Outcomes Consortium (2020) ⁴¹	<p>Muscle weakness defined by low grip strength and slowness defined by low usual gait speed.</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Maximal grip strength <35.5 kg for males, <20 kg for females ▶ Grip strength/BMI <1.05 for males, <0.79 for females ▶ Grip strength/total body fat <1.66 for males, <0.65 for females ▶ Grip strength/arm lean mass <6.1 for males, <3.26 for females ▶ Grip strength/body weight <0.45 for males, <0.34 for females ▶ Gait speed <0.8 m/s
Society on Sarcopenia, Cachexia and Wasting Disorders (2011) ³⁹	<p>Reduced muscle mass, with limited mobility.</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Lean appendicular mass/height² of ≤2 SD below mean of healthy persons between 20 and 30 years of same ethnic group ▶ Walking speed ≤1 m/s or <400 m during 6 min walk
Special Interest Group (2010) ³⁸	<p>Combined presence of low muscle mass and low muscle function defined by low gait speed or well-established functional tests.</p> <p>Cut-offs</p> <ul style="list-style-type: none"> ▶ Muscle mass percentage of ≥2 SD below the mean measured in young adults of the same sex and ethnic background ▶ <0.8 m/s during 4 m walking test

BMI, body mass index.

Table 2 Illustrative search strategy using Medline complete via EBSCOhost

1. AB anxiety OR TI anxiety OR AB anxious OR TI anxious OR (MH "Anxiety") OR (MH "Anxiety Disorders+")
2. AB sarcopen* OR TI sarcopen* OR AB "muscle mass" OR TI "muscle mass" OR AB "lean mass" OR TI "lean mass" OR AB "skeletal mass" OR TI "skeletal mass" OR (MH "Muscular Atrophy+")
3. AB dynapenia OR TI dynapenia OR AB "muscle weakness" OR TI "muscle weakness" OR AB "muscular weakness" OR TI "muscular weakness" OR AB "muscle strength" OR TI "muscle strength" OR AB "muscular strength" OR TI "muscular strength" OR AB "grip strength" OR TI "grip strength" OR AB "handgrip strength" OR TI "handgrip strength" OR (MH "Muscle Strength+") OR (MM "Muscle Strength Dynamometer")
4. AB "gait speed" OR TI "gait speed" OR AB "walking speed" OR TI "walking speed" OR AB "walk test" OR TI "walk test" OR AB "physical performance" OR TI "physical performance" OR AB "timed up and go" OR TI "timed up and go" OR AB "chair stand" OR TI "chair stand" OR AB "limited mobility" OR TI "limited mobility" OR (MM "Walking Speed") OR (MM "Mobility Limitation")
5. 2 OR 3 OR 4
6. 1 AND 5

characteristics; (4) definition and measures of sarcopenia; (5) definition and measures of anxiety; (6) main findings and (7) description of confounders included in the statistical models.

Assessment of methodological quality of included studies

Two reviewers will independently assess the quality of included studies using the study quality assessment tools published by the US National Heart, Lung and Blood Institute.⁴³ Observational study designs will be assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (14 items) and the Quality Assessment of Case–Control Studies (12 items). Clinical trials (baseline data) will be assessed using the Quality Assessment of Controlled Intervention Studies (14 items). We will categorise the overall quality of each study as follows: high ($\geq 70\%$), moderate (40%–69%) or low ($< 40\%$), with a quality rating of low translating to a high risk of bias. Disagreements between reviewers will be resolved through discussion. If unable to reach agreement, final judgement will be provided by a third reviewer.

Data synthesis

Where methodological heterogeneity is low, a meta-analysis will be performed to determine pooled OR for the relationship between sarcopenia and anxiety. If sufficient data are available, we will also conduct subgroup analyses. The groups may be designed based on diagnostic criteria for sarcopenia, sex, age and country. The homogeneity of the OR of the included studies will be assessed using I^2 statistics.⁴⁴ Sources of heterogeneity will be investigated by removing studies at high risk of bias and comparing different study-level methodological characteristics (eg, sarcopenia definition).

If meta-analysis is not possible due to methodological heterogeneity a 'best evidence synthesis' will be performed instead. This method would determine the combined level of evidence, ranging from 'no evidence' to 'strong evidence', as previously described in the musculoskeletal field.^{45 46}

ETHICS AND DISSEMINATION

This systematic review will use published data only and therefore will not require ethical permission. We aim for completion of the review by June 2022. Findings will be disseminated via publication in a peer-reviewed scientific journal as well as through conference presentations.

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