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SYSTEMATIC REVIEW

Risk of secondary sarcopenia in Europeans with fibromyalgia according to the EWGSOP2 guidelines: systematic review and meta-analysis

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ABSTRACT

INTRODUCTION: Fibromyalgia is characterized by chronic widespread pain accompanied by reduced levels of physical activity and associated comorbidities such as overweight and obesity which have been associated to sarcopenia development. The aim of this systematic review is to ascertain whether Europeans with fibromyalgia show a reduction in sarcopenia determinants compared to apparently-healthy controls and to determine the risk of sarcopenia and its possible risk factors (PROSPERO: CRD42023439839).

EVIDENCE ACQUISITION: Systematic searches were conducted on six databases (Academic-Search-Ultimate, CENTRAL, PubMed, SciELO, WOS-Core Collection, and ClinicalTrials.gov last-search February-2024) looking for original studies developed in European countries which assessed any of the sarcopenia determinants proposed by the EWGSOP2-guidelines (handgrip strength, five sit-to-stand, appendicular skeletal mass [ASM], skeletal muscle index [SMI]) and included fibromyalgia and healthy-control individuals. Studies mixing fibromyalgia with other diagnoses were excluded. Random-effects meta-analyses and meta-regressions were used to analyze possible differences and associated risk factors. The risk of bias was assessed using the Cochrane-Rob tool and the Quality Assessment Tool for Observational Studies, and the certainty of the evidence using GRADE-approach.

EVIDENCE SYNTHESIS: A total of 25 studies (6393 individuals; 97% women; 20-65 years) were included. Fibromyalgia individuals showed reduced muscle strength ([handgrip] SMD: -1.16 [-1.29, -1.03]; high-certainty; [five sit-to-stand] not-assessed) and muscle quantity ([ASM] mean-difference: -0.83 kg [-1.41, -0.37]; [SMI] mean-difference: -0.26 kg/m^2 [-0.41, -0.10]; both low-certainty) compared to healthy-controls. Fibromyalgia individuals had nine-times greater risk for probable sarcopenia (OR: 9.23 [6.85, 12.45]; high-certainty), but not for confirmed sarcopenia ([ASM] OR: 0.91 [0.49, 1.67]; [SMI] OR: 0.67 [0.19, 2.33]; both low-certainty) according to the EWGSOP2 cut-off points. Reduced muscle strength was strongly associated to fibromyalgia-severity (β=-0.953 [-0.069, -0.038]). Studies were rated as high-risk of bias overall because did not account for some potential confounders (physical activity, sedentary time, Body Mass Index) which could influence the estimated effect.

CONCLUSIONS: Europeans with fibromyalgia have a large reduction in muscle strength and may have a reduction in muscle quantity. The risk of probable sarcopenia according to the EWGSOP2 cut-off points was nine-times higher, but may have no difference in risk of reduced muscle quantity relative to healthy-controls. Muscle strength was strongly associated to disease severity.

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KEY WORDS: Fibromyalgia; Sarcopenia; Muscle strength; Body composition; Risk factors.

Introduction

Fibromyalgia syndrome is one of the most common musculoskeletal disorders affecting especially middle-aged women. Its estimated prevalence is about 1.8% worldwide and 2.6% in Europe.[1] Although the pathophysiology remains unknown, fibromyalgia is formally recognized as a non-articular chronic rheumatic disease, with an ICD-10-CM Diagnosis Code (M79.7), characterized by muscular tenderness and chronic widespread pain.[2, 3] Individuals with fibromyalgia also suffer from chronic fatigue, cognitive impairment, sleep disturbance, and general somatic discomfort which might contribute to functional decline.[2] Higher sedentary time, reduced levels of physical activity, and associated comorbidities such as overweight and obesity are frequently reported in fibromyalgia individuals.[4-6] These factors impact disease severity[4-6] and are considered critical contributors to sarcopenia development.[7, 8]

Sarcopenia is a progressive and generalized skeletal muscle disorder characterized by loss of both muscle strength and muscle quantity which can lead to adverse health-related consequences including physical disability, falls, hospitalization, and mortality.[9-12] Primary sarcopenia is an age-related disease, but other factors not related to aging such as physical inactivity, sedentary lifestyle or systemic inflammation could predispose to sarcopenia development, also known as secondary sarcopenia.[7, 8] Some comorbidities such as obesity and fibromyalgia per se are characterized by abnormal cytokine profile which leads to a low-grade of systemic inflammation.[4] This imbalance between anti-inflammatory and proinflammatory cytokines can independently lead to a loss of muscle strength and muscle quantity[4, 8] promoting the development of secondary sarcopenia in people with fibromyalgia.

The European Working Group on Sarcopenia in Older People 2 (EWGSOP2) elaborated a consensus to facilitate sarcopenia diagnosis in research and clinical practice. The EWGSOP2 defines probable sarcopenia when a reduction in muscle strength is evident. Then, sarcopenia is confirmed when both muscle strength and quantity are reduced below the established cut-off points.[7] Accordingly, muscle strength can be determined through a handgrip strength test or a five-chair stand test (5STS) while muscle quantity can be measured as appendicular skeletal mass either absolute (ASM) or adjusted for squared-height also named skeletal muscle index (SMI). Although the definition of sarcopenia is still a matter of debate with several definitions proposed, the established cut-off points by the EWGSOP2 guideline have been associated to health-related adverse events[7] and its definition is possibly the most used in research and clinical settings.[13]

Several studies have reported reduced levels of handgrip strength in Europeans with fibromyalgia compared to apparently healthy-matched controls,[14-16] suggesting that these individuals could have a higher risk to develop secondary sarcopenia. However, to our knowledge, no systematic review has previously analyzed whether Europeans with fibromyalgia could predispose to sarcopenia development and if so, what potential factors could be associated with sarcopenia determinants according to the EWSGOP2 guidelines. Providing an exhaustive analysis about the possible risk and potential factors associated to secondary sarcopenia in Europeans with fibromyalgia could help to elaborate specific countermeasures.

Therefore, the aims of this systematic review and meta-analysis were: 1) to ascertain whether Europeans with fibromyalgia show a reduction in sarcopenia determinants compared to healthy-matched controls; 2) to determine the risk of secondary sarcopenia in these individuals, and 3) to analyze possible risk factors which could predispose to secondary sarcopenia according to the EWGSOP2 guidelines.

Evidence acquisition

Design and protocol registration

This systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses[17] and registered on the International Prospective Register of Systematic Reviews (PROSPERO): CRD42023439839

Search strategy and data source

A bibliographic search was performed in the following databases/platforms: PubMed/National Library of Medicine, CENTRAL/Cochrane Library, Academic Search Ultimate/EBSCO host, WOS Core Collection/Web of Science, and SciELO Citation Index/Web of Science. References from included studies were checked looking for potential articles of interest. Additionally, the ClinicalTrials.gov database was consulted for identifying clinical registers. The last search on all sources was run on February 21, 2024. For more information about search strategies see the Supplementary Material (Supplementary Digital Material 1: Supplementary Table I).

Eligibility criteria

Original studies developed in European countries composed by fibromyalgia individuals and a healthy control

TABLE I.—*Sarcopenia determinants and cut-off points recommended by the EWGSOP2 guideline.*

Test	Cut-off points for men	Cut-off points for women
EWGSOP2 sarcopenia cut-off points for low muscle strength by handgrip strength and 5STS test		
Handgrip strength	<27 kg	<16 kg
5STS test	>15 s for five rises	
EWGSOP2 sarcopenia cut-off points for low muscle quantity		
ASM	<20 kg	<15 kg
SMI	<7.0 kg/m^2	<5.5 kg/m^2

5STS: Five-Chair Stand test; ASM: appendicular skeletal mass; SMI: Skeletal Muscle Index.

group which assessed any of the sarcopenia determinants proposed by the EWGSOP2 guidelines were included in this systematic review. The EWGSOP2 guidelines defines muscle weakness using the handgrip strength test or 5STS test and muscle quantity as ASM or SMI (Table I). Studies without enough information to extract outcomes of interest and those mixing fibromyalgia individuals with other diagnoses, such as chronic fatigue syndrome or rheumatoid arthritis were excluded.

Study selection and data extraction

From the initial search, duplicate studies were removed using the Rayyan online software.[18] Then, titles and abstracts were reviewed to exclude any irrelevant study. The study selection was carried out independently by two blinded researchers (LR-L and JDR-C). Disagreements during the study selection were resolved by consensus with a third researcher (MAM-G). Agreement was calculated using Cohen's kappa (κ) coefficient with its 95% confidence interval (95% CI).

Data extraction was performed by a single researcher (LR-L) in a spreadsheet and a second researcher (JDR-C) checked all data extraction point-by-point from the original studies. Data about the characteristics of people with fibromyalgia and the healthy-matched group were extracted (sample size, sex, age, Body Mass Index [BMI], level of physical activity, fibromyalgia severity and its associated questionnaire). Additionally, information about sarcopenia determinants and how these were measured in each study was registered.

Risk of bias and certainty of evidence

Since there is no tool for assessing the risk of bias in this type of systematic review, the Cochrane Collaboration Risk of Bias Tool was used and adapted to the needs of this systematic review. Therefore, domains not relevant such as random sequence generation and allocation concealment were removed and other relevant questions from the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Health Institute were added for assessing selection bias. Specifically, questions such as whether the groups were comparable for the main variables of interest which could influence sarcopenia determinants such as age, sex, BMI, and physical activity level or whether the authors made an appropriate statistical adjustment in their comparisons were added. Performance bias was not relevant in this systematic review since no intervention effect was analyzed. Finally, the risk of bias tool included the following domains; selection bias, detection bias, attrition bias, reporting bias, and other bias. These domains were rated as low risk, high risk or unclear risk of bias.

The certainty of evidence was evaluated using Grading Recommendation Assessment, Development and Evaluation (GRADE) approach and the plain language statements was developed according to GRADE guidelines for informative statements to communicate the findings of systematic reviews.[19]

Statistical analysis

All statistical analyses were performed using RevMan (Review manager [Computer program]. Version 5.4, The Cochrane Collaboration, 2020) and JASP (JASP Team 2023 Version 0.17.2 [Computer software]). The level of statistical significance was set at $P<0.05$. Statistical heterogeneity between studies was assessed visually through the forest plots, the chi-square test and the I^2 statistic which may be interpreted with caution as not important (<40%), moderate (30-60%), substantial (50-90%) and considerable (75-100%). Publication bias was assessed searching clinical trial registers at ClinicalTirals.gov and using the funnel plots and its asymmetry by the Egger's regression test whenever there were a reasonable number of studies (N.>10) included in the meta-analysis.

Objective 1: a set of meta-analyses using a random effect model were performed in order to analyze the possible differences in sarcopenia determinants between fibromyalgia and healthy-matched individuals. Mean differences (MD) or standardized mean differences (SMD) were cal-

culated for each study as well its 95% CI. When median and range were presented, mean and standard deviation were estimated according to the Hozo's Method.[20] The maximal value reported in each study was used for the statistical analysis. Due to the lack of studies analyzing the 5STS test, no meta-analysis was carried out.

Objective 2: in order to analyze whether fibromyalgia individuals have higher odds of secondary sarcopenia compared to their respective counterparts, the number of people for each group who reported measures below the cut-off points established by EWGSOP2 guidelines was calculated. This estimation was performed following the Furukawa's method.[21] Then, the Odds Ratios (ORs) and their 95% CI were calculated for each study. For this meta-analysis, in which homogeneity of measurement units is needed, four studies were excluded because they reported handgrip strength in units other than kilograms and with no possibility of conversion (*i.e.*, conversion from bars to kilograms required information on surface application area).

Objective 3: in order to analyze possible risk factors associated with secondary sarcopenia, a meta-regression was performed using handgrip strength as dependent variable and disease severity as independent variable whereas age, sex, and BMI were used as co-variates. No other sarcopenia determinants were assessed because there were insufficient studies to perform a meta-regression. Additionally, the level of physical activity was not taken into account as an independent variable because only one study used a validated instrument for its measured. Finally, a sensitivity analysis was performed to assess the impact of disease severity on handgrip strength in women, since only one study carried out in men reported disease severity.

Evidence synthesis

Study selection

A total of 208 studies were located in the computerized databases and 31 as registers. From the completed registers (N.=17), a total of six were conducted on European individuals but none of them included a healthy control group. After removing duplicate studies, 158 studies were screened reading title and abstract and 57 met the selection criteria. A total of 20 studies were excluded after reading the full text because they were not carried out on European individuals, one study because it was published as conference abstract and not enough information for data extraction was provided, and six studies did not include a healthy control group. Finally, a total of 25 studies were included in the qualitative and quantitative synthesis (Figure 1). Agreement between researchers during the study selection process was almost perfect (κ: 0.91; 95% CI: 0.83 to 0.99).

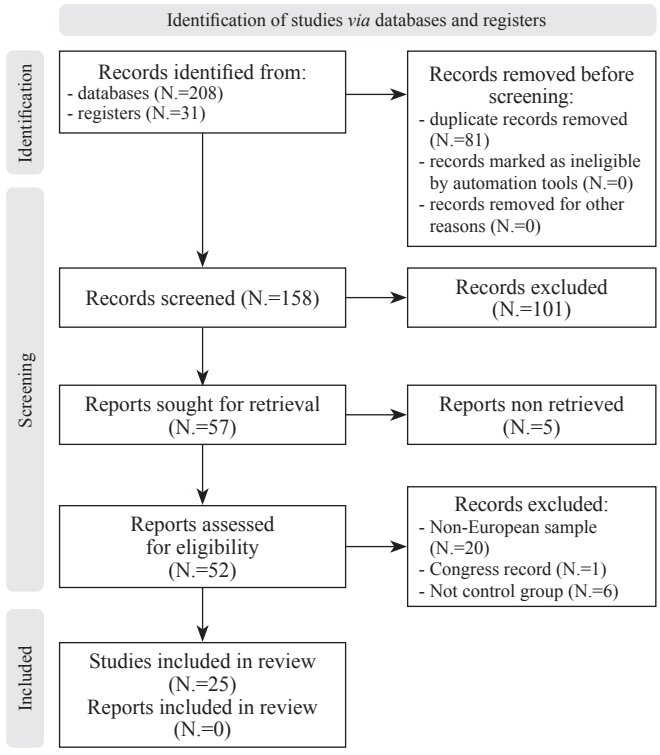

Figure 1.—PRISMA flow diagram.

Study characteristics and risk of bias

The studies included in this review covered a period from 1988 to 2023.[14, 22] Most of them were conducted in Spain (N.=15) and the remaining were conducted in Sweden (N.=4), Finland (N.=2), Norway (N.=1), Italy (N.=1), Belgium (N.=1), and the Netherlands (N.=1).

Selection bias was rated as high risk of bias in all included studies, since the groups were not comparable for the main variables of interest[14, 15, 22-34] or not controlled for physical activity levels.[16, 22, 35-42] Only four studies measured participants' physical activity level,[23, 26, 31, 43] but no clear information was provided on whether the groups were comparable or whether an appropriate adjustment was made. Attrition bias was rated as low risk in all studies, except for one study which was rated as unclear because the authors stated that "only participants with complete data for all the variables were included", but no information was provided about how many participants did not complete these tests.[30]

Blinding of outcome assessment for handgrip strength was considered as low risk only in one study[35] while the remaining studies were rated as unclear risk because not enough information was provided about blinding and muscle testing measurements could be influenced by researcher encouragement. Blinding of outcome assessment for muscle quantity measurements was rated as low risk in all studies.[22, 34, 38-40] Selective reporting was rated as unclear in all included studies since the study protocol was not previously published. Only one study informed about the registered protocol but the sample size and the outcomes measured did not match with the published study.[22] Additionally, one study was rated as high risk of bias because the authors excluded all men due to the small sample size (N.=65) which was considered as a deviation from the non-published protocol.[39] Some studies were rated as unclear risk in other bias since no information about the validity of the instrument nor the validated equation used to estimate muscle quantity was provided[38-40] or the equation used was validated in a different brand device[34] or in a sample with different characteristics[22] as in the validation study (Supplementary Digital Material 2: Supplementary Table II).

Participant characteristics

This systematic review analyzed a total of 6393 participants (97% women) with an age range from 20 to 65 years. A total of 3934 participants were diagnosed with fibromyalgia and 2459 were apparently healthy-control individuals.

Individuals with fibromyalgia were diagnosed by a rheumatologist in all included studies. The diagnosis criteria used were the Yunus Criteria (N.=3) and the American College of Rheumatologists (1990) (N.=14) or its revised version (2010) (N.=6), as well as the updated criteria of 2016 (N.=1). One study did not specified the diagnostic criteria used.[22] Disease severity was assessed through the Fibromyalgia Impact Questionnaire (FIQ) in half of the included studies.[16, 27, 30-32, 34-37, 39, 40, 42] However, thirteen studies did not assess disease severity.[14, 15, 22-26, 28, 29, 33, 38, 41, 43] Although four studies provided some information about the participants' physical activity,[23, 26, 31, 43] only one of them used a previously validated instrument.[31]

People with fibromyalgia were usually categorized as overweight or obese (BMI ≥25 kg/m^2), while healthy-controls were usually categorized as normal weight and overweight (BMI-range: 23.13 to 30.2 kg/m^2). Several studies did not describe the BMI of the participants (N.=7), while two of them indicated that the fibromyalgia group had significantly a higher BMI than the healthy-control group but no values were provided.[31, 33] Only one study reported a higher BMI for the healthy-control group than the fibromyalgia group.[27]

Outcome characteristics: sarcopenia determinants

Muscle strength determinants: handgrip strength test and 5STS test

Handgrip strength was measured in 24 of 25 studies included in this systematic review, but the measurements were very heterogeneous across studies. Most studies performed the evaluation in a standing position with the elbow extended and the shoulder flexed at 30° from the trunk, while two studies performed the evaluation in a sitting position with the elbow flexed at 90°, wrist in a neutral position and thumb facing upwards.[23, 42] Seven studies did not specify the measurement position,[14, 24, 30-34] two of them only commented that the participants were in the sitting or most comfortable position.[14, 33] Two or three trials with each arm were usually performed. Most studies used the average of the best score from the right and left hand, whereas seven studies used the higher value of a set of muscle contractions for their analysis.[14, 22, 23, 25, 26, 35, 41] The results were reported in kilograms of force (N.=16), newtons (N.=4), millimeters of mercury (N.=2), and kilopascals (N.=2). Most studies performed the test using a Takei or JAMAR dynamometer, while six articles used a strain gauge, vigorimeter or cylindrical grip device.[14, 15, 24-26, 42] Values from each study are reported in Supplementary Digital Material 3 (Supplementary Table III).

No studies measured the 5STS test.

Muscle quantity determinants: ASM and SMI

Five studies measured ASM through bioelectrical impedance analysis.[22, 34, 38-40] Fibromyalgia individuals showed ASM in a range of 22.7–23.95 kg, while the healthy group showed a range of 23-25.76 kg. From the aforementioned studies, two of them[34, 40] also reported SMI measurements in a range of 7.2-9.3 kg/m^2 and 7.4-9.4 kg/m^2 for fibromyalgia and healthy individuals, respectively.

Objective 1: differences in sarcopenia determinants

Considering muscle strength as the primary determinant of sarcopenia, our meta-analysis found that Europeans with fibromyalgia showed a large reduction in handgrip strength compared to apparently healthy-matched controls (SMD: -1.16; 95% CI: -1.29 to -1.03; high certainty of evidence),

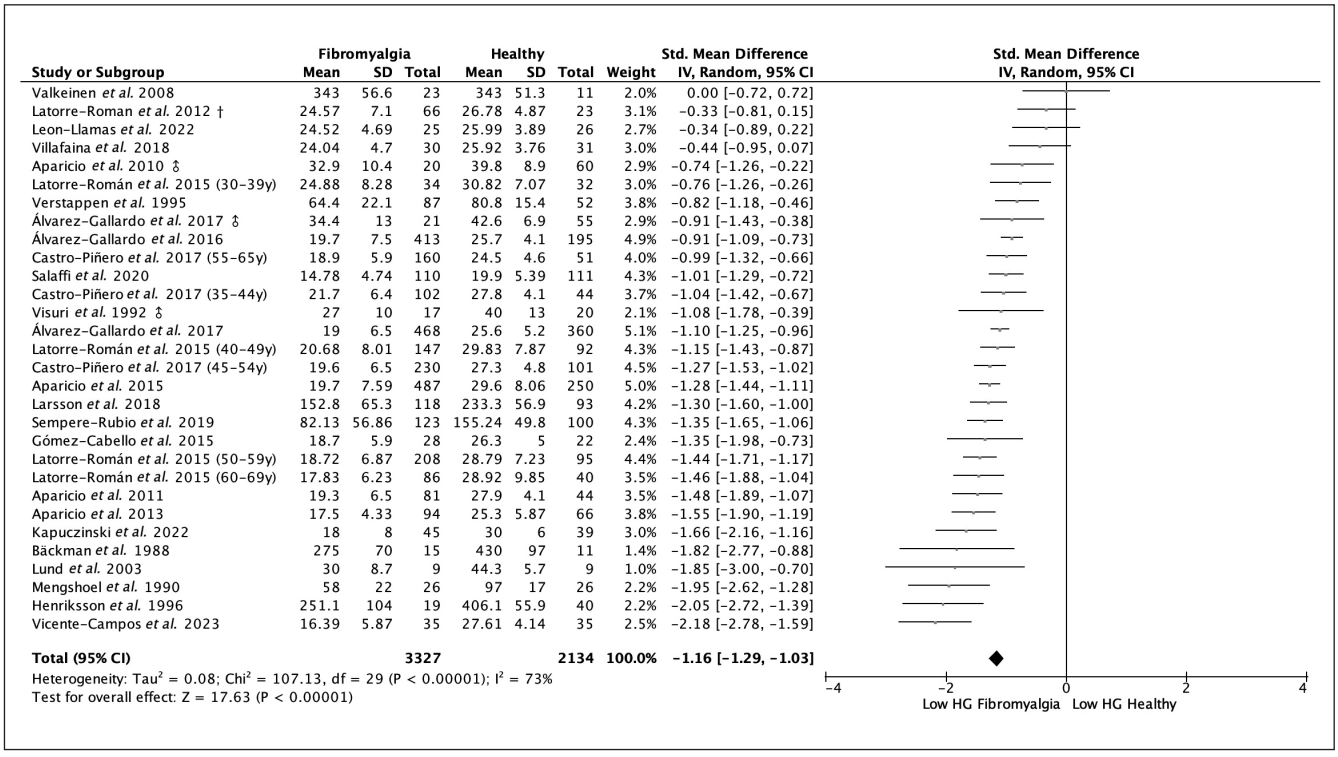

Figure 2.—Forest plot of comparison: fibromyalgia *versus* healthy, outcome: handgrip strength (HG). All studies were conducted in women unless otherwise specified (♂).[14, 15, 22-37, 39-43]
† Data from subgroup analysis was pooled into a single fibromyalgia group.

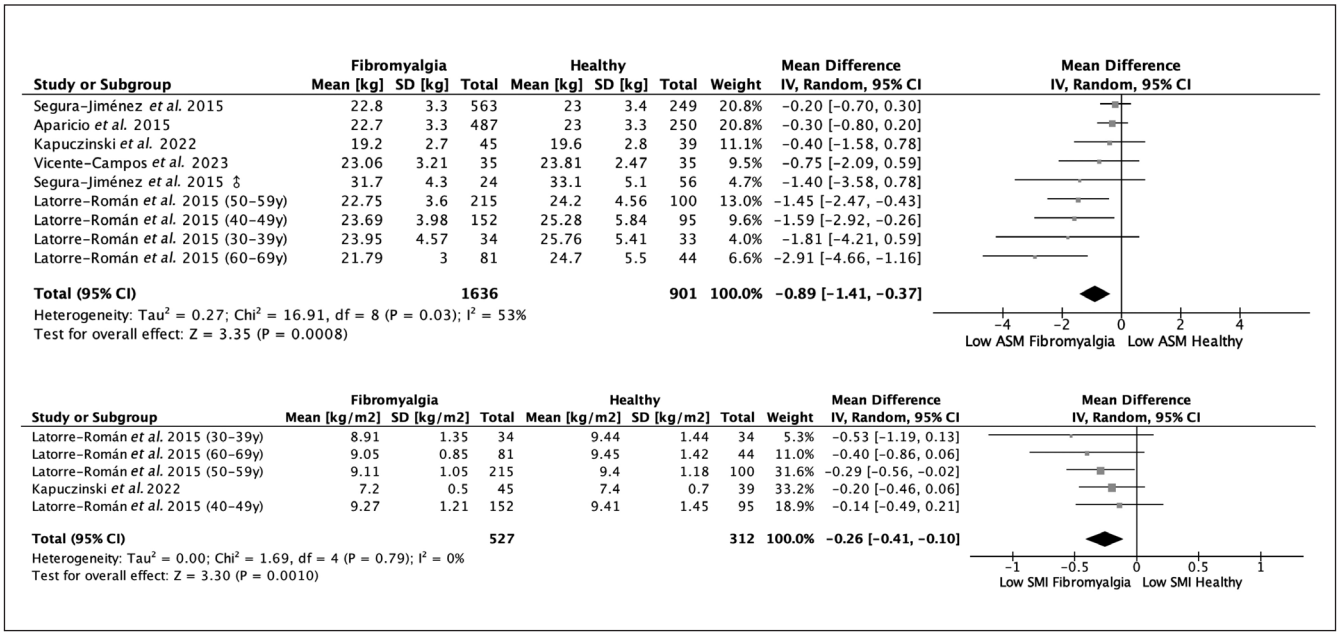

Figure 3.—Forest plot of comparison: fibromyalgia *versus* healthy, outcome: appendicular skeletal mass (ASM) in kg (upper panel). Skeletal muscle index (SMI) in kg/m² (lower panel). All studies were conducted in women unless otherwise specified (♂).[22, 34, 38-40]

with substantial heterogeneity and absence of publication bias (Supplementary Digital Material 4: Supplementary Figure 1). Among the 30 comparisons, only four of them did not show differences in handgrip strength (Supplementary Digital Material 5: Supplementary Figure 2). After a subgroup analysis adjusting for disease severity as measured by the FIQ, the test for heterogeneity (I^2) changed from 73% to 0%. Therefore, the certainty of the evidence was not downgraded due to heterogeneity but due to serious risk of bias, and it was upgraded due to the large magnitude of the effect (Supplementary Digital Material 6: Supplementary Table IV). Since no studies analyzed the 5STS test, neither qualitative nor quantitative analysis was carried out (Figure 2).[14, 15, 22-37, 39-43]

Regarding muscle quantity as the secondary determinant of sarcopenia, a slight reduction in both ASM (MD: -0.89 kg; 95% CI: -1.41 to -0.37; low certainty of evidence) and SMI (MD: -0.26 kg/m^2; 95% CI: -0.41 to -0.10; low certainty of evidence) was found in Europeans with fibromyalgia compared to apparently healthy-matched controls, with moderate heterogeneity for ASM and absence for SMI (Figure 3).[22, 34, 38-40] There was no suspicion of publication bias (Supplementary Digital Material 7: Supplementary Figure 3, 4). The certainty of the evidence was downgraded due to a very serious risk of bias.

Objective 2: risk of secondary sarcopenia

Europeans with fibromyalgia were nine times increased risk of probable sarcopenia according to the EWGSOP2 guidelines (*i.e.*, reduced handgrip strength below the specific cut-off points) compared to apparently healthy-matched controls (OR: 9.23; 95% CI: 6.85 to 12.45; high certainty of evidence), with absence of both heterogeneity and publication bias (Figure 4).[16, 22, 25-37, 39-43] The certainty of the evidence was downgraded due to a serious risk of bias and upgraded due to the large magnitude of the effect.

Regarding muscle quantity, no differences in risk of low absolute muscle quantity (ASM) (OR: 0.91; 95% CI: 0.49 to 1.67; low certainty of evidence) neither in risk of low relative muscle quantity (SMI) (OR: 0.67; 95% CI: 0.19 to 2.33; low certainty of evidence) were found between Europeans with fibromyalgia and healthy-matched controls

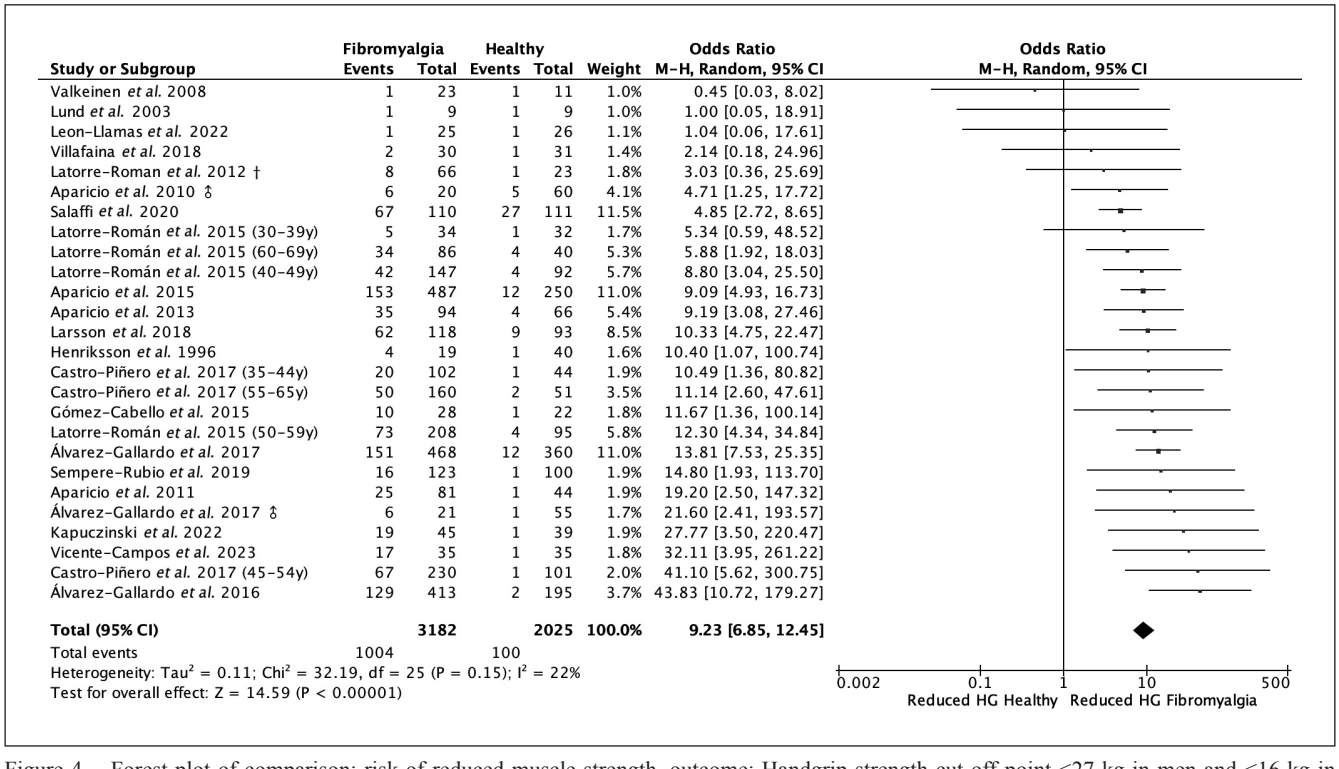

Figure 4.—Forest plot of comparison: risk of reduced muscle strength, outcome: Handgrip strength cut-off point <27 kg in men and <16 kg in women. All studies were conducted in women unless otherwise specified (♂).[16, 22, 25-37, 39-43]
† Data from subgroup analysis was pooled into a single fibromyalgia group.

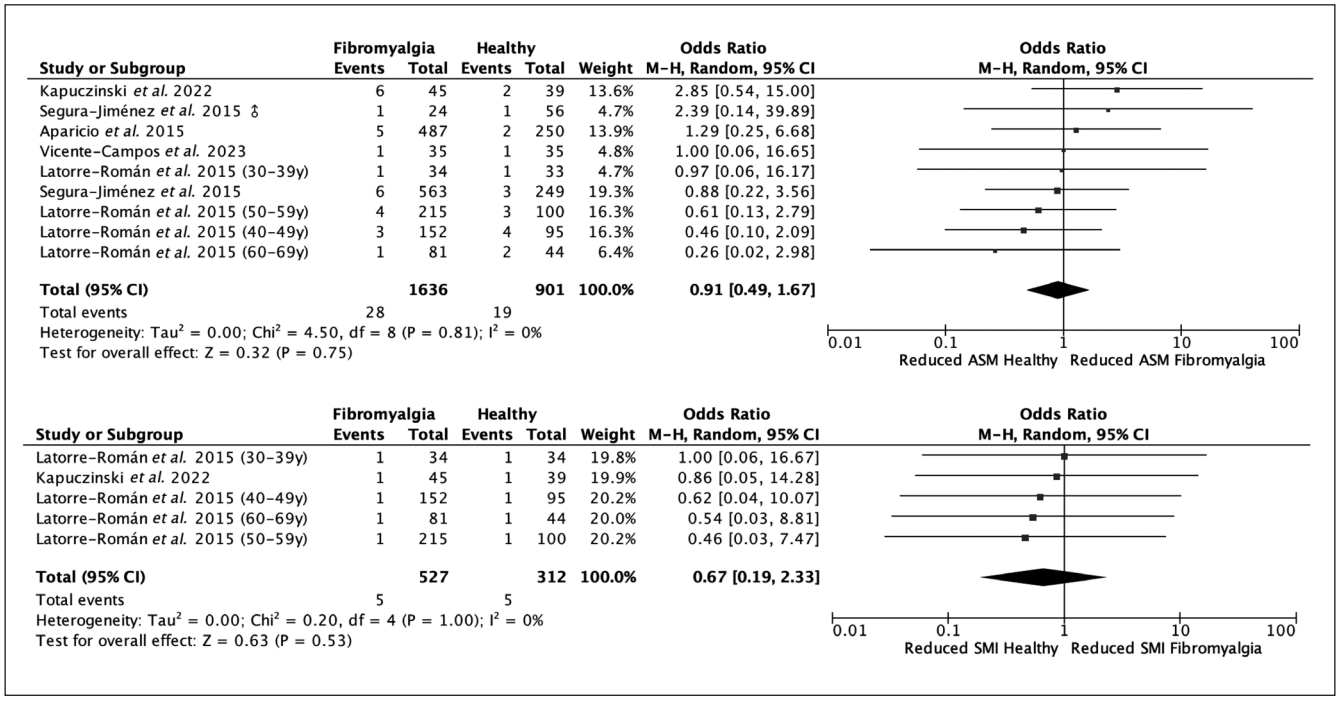

Figure 5.—Forest plot of comparison: risk of reduced absolute muscle quantity, outcome: appendicular skeletal mass (ASM) cut-off point <20 kg in men and <15 kg in women (upper panel). Skeletal Muscle Index (SMI) cut-off point <5.5 kg/m² in women (lower panel). All studies were conducted in women unless otherwise specified (♂).[22, 34, 38-40]

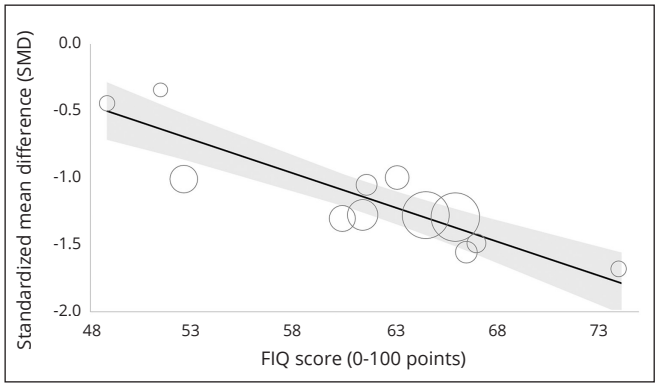

Figure 6.—Meta-regression bubble plot for the association between differences in handgrip strength and disease severity as measured by the Fibromyalgia Impact Questionnaire (FIQ) with its 95% confidence interval represented by grey shade. The bubbles represent the standardized mean difference (SMD) for 12 comparisons that reported disease severity and their size are directly proportional to their precision. Sensitivity analysis after removing one study conducted in men.

(Figure 5).[22, 34, 38-40] There was absence of heterogeneity and no suspicion of publication bias (Supplementary Digital Material 8: Supplementary Figure 5, 6). The certainty of the evidence was downgraded due to a very serious risk of bias (Supplementary Table IV).

Objective 3: risk factors associated to secondary sarcopenia

Differences in handgrip strength between Europeans with fibromyalgia and healthy-matched controls were associated with disease severity as measured by the FIQ (β=-0.865; 95% CI: -0.071 to -0.029; N.=13 comparisons). After a sensitivity analysis removing the only study conducted in men, this association was stronger (β=-0.953; 95% CI: -0.069 to -0.038; N.=12 comparisons) (Figure 6). Co-variates such as age and BMI were not associated to differences in handgrip strength between group comparisons. Physical activity level was not introduced into the model due to lack of data. No other meta-regressions were conducted due to low number of comparisons available (N.<10 comparisons).

Discussion

Results from our meta-analyses showed a large reduction in handgrip strength in Europeans with fibromyalgia compared to apparently healthy-matched controls. In fact, only four from a total of the 30 comparisons did not show between-group differences in handgrip strength. The reductions in handgrip strength were below the specific cut-off points provided by the EWGSOP2 guidelines in

most of the comparisons analyzed. Our estimated risk of developing probable sarcopenia was nine times greater in Europeans with fibromyalgia. In other words, about 273 more per 1000 individuals would develop probable sarcopenia due to fibromyalgia compared to apparently healthy people. However, although Europeans with fibromyalgia also showed a reduction in muscle quantity, the pooled estimated difference was minimal (~0.9 kg and ~0.3 kg/m^2) and no increased risk of reduced muscle quantity was found.

Considering the definition of sarcopenia provided by the EWGSOP2 guidelines, these results support the notion that Europeans with fibromyalgia could be predisposed to develop probable sarcopenia but not confirmed sarcopenia (*i.e.,* reduced both muscle strength and quantity). However, the findings reported from muscle quantity outcomes (ASM and SMI) should be interpreted with caution due to the low certainty of the evidence. Few studies (N.=5) analyzed muscle quantity and all of them used bioelectrical impedance analysis. This technique is considered safe, inexpensive and useful for measuring muscle quantity,[44] particularly in clinical settings where reference standards (computed tomography and magnetic resonance imaging) are constrained. However, this technique usually underestimates fat mass and overestimates muscle mass compared to the reference standards,[44] especially in overweight or obese individuals who have shown an overestimation of muscle mass of ~3 kg (range 1.0-5.2 kg).[45] In order to overcome this gap, equations have been generated based on factors such as age, sex, height, and weight, allowing the accurate estimation of muscle quantity.[44] In our systematic review, most studies did not use validated equations to estimate muscle quantity and did not provide information on the validity of the instrument used.[38-40] Some of them stated that the measures showed acceptable test-retest reliability[38, 40] which could be adequate for detecting changes over-time but not for establishing a diagnostic based on specific cut-off points. Moreover, all studies included Europeans with fibromyalgia with a higher BMI relative to the healthy control group. In fact, most of them were categorized as overweight (36%) and obese (39%), whereas healthy individuals were categorized as normal-weight (36%) and overweight (41%). These between-group differences may impact on the precision of the estimated muscle quantity, especially in those scenarios where a validated equation was not used and/or the validity of their measures is unknown. This is noteworthy since various studies using ultrasonography have reported reduced muscle thickness and cross-sectional area of several muscle groups in fibromyalgia compared to apparently healthy individuals, such as quadriceps femoris, tibialis anterior, biceps and triceps brachii, among others.[46, 47] Even if a validated equation is used, when individuals have an elevated BMI, it might be more appropriate to adjust muscle quantity by body weight (ASM/W) or BMI (ASM/BMI) rather than by squared-height (SMI),[8, 48, 49] because individuals with obesity may conversely have comparable or even higher absolute muscle quantity relative to their non-obese counterparts due to higher overall body mass.[8] In these circumstances, where individuals have co-existence of excess adiposity and low muscle quantity and strength, the recent consensus statement for diagnosing sarcopenia obesity should be used.[8] Accordingly, adjusting muscle quantity by body weight may have relevant clinical and functional consequences, even in the absence of absolute muscle quantity reduction.[8, 48] Several studies have reported greater amount of fat mass and reduced muscle strength in Europeans with fibromyalgia compared to their healthy-counterpart, despite the absence of differences in absolute muscle quantity.[22, 28, 38, 39] These results highlight the need for assessing sarcopenia obesity through validated procedures and specific cut-off points in order to not underestimate the possible risk of developing secondary sarcopenia in these individuals.

Obesity is an aggravating comorbid condition frequently reported in people with fibromyalgia which negatively affects fibromyalgia severity.[4] Moreover, fibromyalgia severity has been associated with reduced levels of physical activity and sedentary lifestyle[5, 6] which are considered risk factors for developing obesity and sarcopenia.[4, 7, 8, 50] This coexistence generates a vicious circle between physical inactivity, fat gain and muscle loss which leads to dependency, disability[4, 7, 8] and increased risk of mortality.[51, 52] Although physical activity was not reported in most of the included studies, fibromyalgia severity was strongly associated to reduced handgrip strength (β=-0.865), regardless of age and BMI. However, we cannot be confident that disease severity was a risk factor for the development of probable sarcopenia in Europeans with fibromyalgia, since cross-sectional associations do not allow causal relationships between variables and other confounding factors such as physical activity or sedentary time were not taken into account due to lack of data. Similarly, we could not analyze the risk factors associated with reduced muscle quantity due to the limited number of studies.

Handgrip strength has traditionally been used to measure muscle strength in the evaluation of sarcopenia,[13] however sarcopenia prevalence may change when using

upper limb (handgrip strength) compared to lower limb (5STS) measures. Several studies using the EWGSOP2 guidelines for sarcopenia diagnosis have reported a prevalence of more than two-fold using 5STS compared to the handgrip strength test in European community-dwelling older adults.[11, 53] This is of considerable importance because it has recently been reported that some European individuals diagnosed with sarcopenia using the 5STS test were categorized as healthy when the handgrip strength test was used.[11, 53] These findings suggest that the criteria provided by the EWGSOP2 guidelines are not interchangeable and highlight the importance of assessing both upper- and lower-limb muscle strength for sarcopenia diagnosis in research and clinical practice. The 5STS is considered a practical, reliable and valid functional test, particularly when space and time are constricted. This test has been also considered a good predictor of future disability, falls, mobility limitation, frailty and even mortality in community-dwelling older adults.[54-56] It should be noted that no studies included in this systematic review used the 5STS test as a surrogate measure of lower limb muscle strength. However, some of them used a modified version which take into account the number of repetitions performed during the time period of 30 s chair-stand test. Remarkably, all of them found significant differences (MD: -4.7 repetitions; 95% CI: -5.6 to -3.8; data not shown) between Europeans with fibromyalgia and their healthy counterpart,[27, 29, 30, 37, 39-41] so these differences may be considered as important due to its magnitude (SMD: -2.05; 95% CI: -2.5 to -1.6; data not shown). Nevertheless, these results, although interesting, were outside the scope of this systematic review because no specific cut-off point for sarcopenia diagnosis is available. Further studies should consider examining reduced performance on the 5STS test in Europeans with fibromyalgia because loss of muscle strength during aging is usually greater in the lower limb than upper limb muscles[57, 58] which may potentially predispose to a greater risk of probable sarcopenia than the risk estimated in our systematic review based on handgrip strength.

Sarcopenia is a progressive skeletal muscle disorder associated with health risks such as physical dysfunction, falls, fractures, hospitalization, and mortality.[9-12] Since dynamic transitions exist between different sarcopenia statuses, probable sarcopenia identification has been proposed as a critical time window to promote sarcopenia reversion.[59] Thus, early screening for sarcopenia in fibromyalgia individuals could potentially reduce the incidence of adverse-health related consequences, inform about prognosis, and reduce healthcare cost. In fact, resistance training has been proposed as the best intervention for reversing sarcopenia in older adults,[60] but also it has demonstrated a more favorable effect compared to other forms of exercises on the impact of fibromyalgia.[61] Therefore, based on best-quality evidence and clinical reasoning, people with fibromyalgia could potentially reduce its risk of developing sarcopenia performing resistance training with a relatively high degree of effort for 1-3 sets of 6-12 repetitions twice a week.[60, 62] However, further studies are needed to confirm this statement.

Limitations of the study

Despite a rigorous approach towards data collection and synthesis, this review is not without limitations. All analyses were based on cross-sectional data which do not allow causal relationships between variables. Moreover, most of the included studies did not account for some potential confounders such as physical activity, sedentary time, BMI, and depression, which could potentially influence the magnitude of the estimated effect, especially on reduced muscle quantity. For example, a recent systematic review and meta-analysis showed that obesity was associated with 34% reduced risk of sarcopenia, however after adjusting obesity for muscle mass the estimated risk of sarcopenia in people with obesity was three-fold higher than the non-obese counterparts.[63] Unfortunately, our meta-analyses on muscle quantity outcomes could not be adjusted for some potential confounders due to the small number of studies included. Reduced levels of physical activity is one of the main risk factors for sarcopenia development,[64] therefore future studies should take into account physical activity levels through validated instruments to better understand the underlying mechanisms of reduced both muscle strength and quantity in people with fibromyalgia. Finally, our estimated risk of sarcopenia was based on the cut-off points proposed by the EWGSOP2 guidelines which have been associated to health-related adverse events.[7] However, an important question that remains is whether the use of a different clinical definition for sarcopenia changes our risk estimated and the association to negative health-related events.

To our knowledge, this is the first systematic review to provide an exhaustive analysis about the possible risk and potential factors associated with secondary sarcopenia in Europeans with fibromyalgia. Knowing the risk of sarcopenia development and its associated factors is essential to elaborate specific countermeasures. This comprehensive

analysis also highlighted some important methodological issues and gaps on sarcopenia assessment and provided some advices for further studies on this topic.

Conclusions

Europeans with fibromyalgia have a large reduction in muscle strength and may have a slight reduction in muscle quantity relative to apparently healthy individuals. The estimated risk of probable sarcopenia according to the EWGSOP2 cut-off points was nine times higher in this population, but may have no difference in the risk of reduced muscle quantity relative to apparently healthy controls. The large reduction in muscle strength was strongly associated to disease severity.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Laura Rodríguez-Lumbreras: conceptualization, search strategies, selection process, data extraction, risk of bias assessment, writing – review and editing. Juan D. Ruiz-Cárdenas: conceptualization, protocol registration, search strategies, selection process, data extraction verification, risk of bias assessment, statistical analysis, supervision, writing – review and editing. María A. Murcia-González: conceptualization, formal analysis, selection process, risk of bias assessment, supervision, writing – review and editing. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Search strategies.

Database / Platform	Syntaxis
Pubmed / National Library of Medicine	((Fibromyalgia[tw]) AND (5STS[tw] OR "five chair-stand"[tw] OR "5 chair-stand"[tw] OR "5-time chair stand"[tw] OR "5-times sit-to-stand"[tw] OR "five-times sit-to- stand"[tw] OR "5 sit-to-stand"[tw] OR "Five sit-to-stand"[tw] OR handgrip[tw] OR "grip strength"[tw] OR "grip force"[tw] OR "skeletal muscle index"[tw] OR "appendicular skeletal mass"[tw] OR "appendicular muscle mass"[tw] OR "appendicular skeletal muscle mass"[tw] OR "appendicular lean mass"[tw])) AND (healthy[tw] OR controls[tw] OR matched[tw] OR counterpart[tw] OR non- fibromyalgia[tw])
CENTRAL / Cochrane Library	#1 ("fibromyalgia") #2 ("5STS" OR "five chair-stand" OR "5 chair-stand" OR "5-times chair stand" OR "5-times sit-to-stand" OR "five-times sit-to-stand" OR "5 sit-to-stand" OR "five sit-to-stand" OR "handgrip" OR "grip strength" OR "grip force" OR "skeletal muscle index" OR "appendicular skeletal mass" OR "appendicular muscle mass" OR "appendicular skeletal muscle mass" OR "appendicular lean mass") #3 (healthy OR controls OR matched OR counterpart OR non-fibromyalgia) #1 AND #2 AND #3
Academic Search Ultimate / EBSCO host	((Fibromyalgia) AND (5STS OR "five chair-stand" OR "5 chair-stand" OR "5-time chair stand" OR "5-times sit-to-stand" OR "five-times sit-to-stand" OR "5 sit-to-stand" OR "Five sit-to-stand" OR handgrip OR "grip strength" OR "grip force" OR "skeletal muscle index" OR "appendicular skeletal mass" OR "appendicular muscle mass" OR "appendicular skeletal muscle mass" OR "appendicular lean mass")) AND (healthy OR controls OR matched OR counterpart OR non-fibromyalgia)
WOS Core Collection / Web of Science	TS=((Fibromyalgia) AND (5STS OR "five chair-stand" OR "5 chair-stand" OR "5-time chair stand" OR "5-times sit-to-stand" OR "five-times sit-to-stand" OR "5 sit-to-stand" OR "Five sit-to-stand" OR handgrip OR "grip strength" OR "grip force" OR "skeletal muscle index" OR "appendicular skeletal mass" OR "appendicular muscle mass" OR "appendicular skeletal muscle mass" OR "appendicular lean mass") AND (healthy OR controls OR matched OR counterpart OR non-fibromyalgia))
SciELO / Web of Science	TS=((Fibromyalgia) AND (5STS OR "five chair-stand" OR "5 chair-stand" OR "5-time chair stand" OR "5-times sit-to-stand" OR "five-times sit-to-stand" OR "5 sit-to-stand" OR "Five sit-to-stand" OR handgrip OR "grip strength" OR "grip force" OR "skeletal muscle index" OR "appendicular skeletal mass" OR "appendicular muscle mass" OR "appendicular skeletal muscle mass" OR "appendicular lean mass") AND (healthy OR controls OR matched OR counterpart OR non-fibromyalgia))
ClinicalTrials.gov / National Library of Medicine	(Fibromyalgia) AND (5STS OR "five chair-stand" OR "5 chair-stand" OR "5-time chair stand" OR "5-times sit-to-stand" OR "five-times sit-to-stand" OR "5 sit-to-stand" OR "Five sit-to-stand" OR handgrip OR "grip strength" OR "grip force" OR "skeletal muscle index" OR "appendicular skeletal mass" OR "appendicular muscle mass" OR "appendicular skeletal muscle mass" OR "appendicular lean mass")

SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table II.—Risk of bias of each study.

Bäckman *et al.* (1988)[14]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, but body mass index and physical activity level were not taken into account. The authors said that "there was no difference regarding age between fibromyalgia patients and controls." but no data about testing was provided.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear risk	No information on the validity of the outcome measure.
Mengshoel *et al.* (1990)[23]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, but body mass index and physical activity level were not taken into account. The authors recruited "age-matched females" but no information about control group age nor between-group testing was provided.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Visuri *et al.* (1992)[24]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Although it seems that groups were similar according to age, weight and height, no data about testing was provided. Additionally, physical activity level was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Verstappen *et al.* (1995)[15]		
Bias	**Authors'**	**Support for judgement**

	judgement	
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex and age, but not for body mass index which was lower in the control group. No adjustment was performed between-groups comparison for body mass index. Physical activity was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Henriksson *et al.* (1996)[25]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex and age. The authors said that "no significant weight or age differences were found" but no data about testing was provided. Body mass index and physical activity level were not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published. Authors said "thirty-seven age-matched healthy women were used as a reference group", but the reference group was composed by 40 participants (see Table IV in Henriksson *et al.*)
Other bias	Unclear risk	No information on the validity of the outcome measure.
Lund *et al.* (2003)[26]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	It seems that groups were similar according to age, weight and height, but no data about testing was provided. Although physical activity level was measured, no clear information about whether the groups were comparable or appropriate adjustment was provided.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear risk	No information on the validity of the outcome measure.
Valkeinen *et al.* (2008)[43]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment	High risk	Groups were comparable by sex, weight, and body mass index. Although physical activity

(selection bias)		level was measured, it was not used as covariable for between-group comparisons.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear risk	No information on the validity of the outcome measure.
Aparicio *et al.* (2010)[36]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, weight, height, and body mass index. We rated "high risk of bias" because physical activity level was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Aparicio *et al.* (2011)[16]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, weight, height, and body mass index. We rated "high risk of bias" because physical activity level was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Latorre-Román *et al.* (2012)[37]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, weight, and body mass index. We rated "high risk of bias" because physical activity level was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear risk	No information on the validity of the outcome measure.
Aparicio *et al.* (2013)[27]		

Bias	Authors' judgement	Support for judgement
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, but not for age, weight, height, and body mass index. Although an appropriate adjustment was performed for age, body mass index and other possible confounders for handgrip strength between-group comparisons, physical activity was not taken into account. Additionally, between-groups differences in body mass index could lead to overestimation of muscle mass in the fibromyalgia group.
Blinding of outcome assessment (detection bias)	Unclear risk / Low risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors, thus it was rated as unclear risk. However, blinding probably does not affect muscle mass measurements, thus it was rated as low risk.
Incomplete outcome data (attrition bias)	Low risk	A total of 11 participants did not complete all physical fitness test. Although, there is no information about how many participants did not complete the fitness tests in each group, the low relative rate of incomplete outcome data was rated as low risk.
Selective reporting (reporting bias)	High risk	Two reasons were used to judge reporting bias. Authors stated 1) "Finally, we decided to exclude 65 men (21 with fibromyalgia and 44 control men) from the present data analysis because of the small sample size of the recruited males with fibromyalgia.", and 2) "To ensure that all tests had the same statistical power, only those subjects who had valid data in all physical fitness tests were included in the analyses."
Other bias	Low risk	No other sources of bias.
Segura-Jiménez *et al.* (2015)[38]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, but not for age, body mass index and weight with the exception of men. Although an appropriate adjustment was performed for age and height, physical activity was not taken into account. Additionally, between-groups differences in body mass index could lead to overestimation of muscle mass in the fibromyalgia group.
Blinding of outcome assessment (detection bias)	Low risk	No information about blinding, but probably blinding does not affect the outcome measure.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear risk	No information about the validity of muscle quantity measures.
Aparicio *et al.* (2015)[39]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, but not for age, weight, height, and body mass index. Although an appropriate adjustment was performed for age, body mass index and other possible confounders for handgrip strength between-group comparisons, physical activity was not taken into account. Additionally, between-groups differences in body mass index

		could lead to overestimation of muscle mass in the fibromyalgia group.
Blinding of outcome assessment (detection bias)	Unclear risk / Low risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors, thus it was rated as unclear risk. However, blinding probably does not affect muscle mass measurements, thus it was rated as low risk.
Incomplete outcome data (attrition bias)	Low risk	A total of 11 participants did not complete all physical fitness test. Although, there is no information about how many participants did not complete the fitness tests in each group, the low relative rate of incomplete outcome data was rated as low risk.
Selective reporting (reporting bias)	High risk	Two reasons were used to judge reporting bias. Authors stated 1) "Finally, we decided to exclude 65 men (21 with fibromyalgia and 44 control men) from the present data analysis because of the small sample size of the recruited males with fibromyalgia.", and 2) "To ensure that all tests had the same statistical power, only those subjects who had valid data in all physical fitness tests were included in the analyses."
Other bias	Unclear risk	No information about the validity of muscle quantity measures.
Latorre-Román *et al.* (2015)[40]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, but not for body mass index. Although an appropriate adjustment was performed for body mass index and other possible confounders for handgrip strength between-group comparisons, physical activity was not taken into account. Additionally, between-groups differences in body mass index could lead to overestimation of muscle mass in the fibromyalgia group.
Blinding of outcome assessment (detection bias)	Unclear risk / Low risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors, thus it was rated as unclear risk. However, blinding probably does not affect muscle mass measurements, thus it was rated as low risk.
Incomplete outcome data (attrition bias)	Low risk	Missing data was balanced between-groups.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear	No information about the validity of muscle quantity measures.
Gómez-Cabello *et al.* (2015)[28]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, but not for body mass index. No adjustment for body mass index was done in muscle strength between-groups comparison. Additionally, physical activity was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.

Other bias	Low risk	No other sources of bias.
Álvarez-Gallardo *et al.* (2016)[29]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, but not for body mass index. No adjustment for body mass index was done in muscle strength between-groups comparison. Additionally, physical activity was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Álvarez-Gallardo *et al.* (2017)[41]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, and body mass index, but physical activity was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Castro-Piñero *et al.* (2017)[30]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, but not for height. Additionally, no information about age, body mass index, and physical activity was given. It is probable that groups were not comparable for these variables and that appropriate adjustment was not done.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Unclear risk	Authors stated "only participants with complete data for all the variables were included.", but no information about how many participants did not complete these tests is provided.
Selective reporting (reporting bias)	High risk	Three reasons were used to judge reporting bias. Authors stated 1) "Men were also excluded because of the small sample size (n = 86, 26 men with fibromyalgia)", 2) "only participants with complete data for all the variables were included.", 3) "Thus, the final study sample comprised 488 women with fibromyalgia vs. 200 controls.", but data from 496 women with fibromyalgia and 196 controls is provided in Table I of this study.

Other bias	Low risk	No other sources of bias.
Larsson *et al.* (2018)[31]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, but not for body mass index and physical activity level. Additionally, no appropriate adjustments were done for muscle strength between-group comparison.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Authors stated "This is a sub-study of a multi-center experimental study that enrolled women with FM and healthy women (ClinicalTrials.gov identification number: NCT01226784)", but the outcome measures in that protocol did not match with the actual study. There is no information about handgrip strength test in the study protocol.
Other bias	Low risk	No other sources of bias.
Villafaina *et al.* (2018)[32]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, but not for body mass index. Additionally, physical activity level was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Sempere-Rubio *et al.* (2019)[33]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, but not for body mass index. Additionally, physical activity level was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear risk	No information on the validity of the outcome measure.
Salaffi *et al.* (2020)[42]		
Bias	**Authors'**	**Support for judgement**

	judgement	
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, and body mass index. However, physical activity level was not taken into account.
Blinding of outcome assessment (detection bias)	Unclear risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear risk	No information on the validity of the outcome measure.
Kapuczinski *et al.* (2022)[34]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex and height, but not for age and body mass index. Additionally, physical activity level was not taken into account and between-groups differences in body mass index could lead to overestimation of muscle mass in the fibromyalgia group.
Blinding of outcome assessment (detection bias)	Unclear risk / Low risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors, thus it was rated as unclear risk. However, blinding probably does not affect muscle mass measurements, thus it was rated as low risk.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Unclear risk	Since equations are only valid for the same bioelectrical impedance analysis device as in the validation study, we rated it as unclear risk.
Leon-Llamas *et al.* (2022)[35]		
Bias	**Authors' judgement**	**Support for judgement**
Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, height, weight, and body mass index. However, physical activity level was not taken into account.
Blinding of outcome assessment (detection bias)	Low risk	Authors stated "The researcher who evaluated the physical fitness tests was blinded to group allocation. The participants were called to perform the physical tests on their assigned day. However, the researcher did not know the group to which the participants belonged, since he was only focused on evaluating."
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol published.
Other bias	Low risk	No other sources of bias.
Vicente-Campos *et al.* (2023)[22]		
Bias	**Authors' judgement**	**Support for judgement**

Comparable groups or appropriate adjustment (selection bias)	High risk	Groups were comparable by sex, age, and height but not for weight and body mass index. Additionally, physical activity level was not taken into account and between-groups differences in body mass index could lead to overestimation of muscle mass in the fibromyalgia group.
Blinding of outcome assessment (detection bias)	Unclear risk / Low risk	No information about blinding. Strength testing may have been influenced by motivation from unblinded assessors, thus it was rated as unclear risk. However, blinding probably does not affect muscle mass measurements, thus it was rated as low risk.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	Authors stated, "The research was registered in www.clinicaltrials.gov (NCT05362396)." However, the sample size and the outcomes provided in the register did not match with the study published.
Other bias	Unclear risk	Since the bioelectrical impedance analysis device is only valid in a sample with similar characteristics as in the validation study, we rated it as unclear risk.

SUPPLEMENTARY DIGITAL MATERIAL 3

Supplementary Table III.—Characteristics of the included studies (N.=25).

Autor (year) / Country	Participants	Muscle strength		Muscle quantity	
		Handgrip strength	5STS test (s)	ASM (Kg)	SMI (Kg/m^2)
Bäckman *et al.* (1988) / Sweden[14]	FM: 15 W; 47.8 (30–66) yrs. BMI: n/m Severity: n/m	275 (70) mmHg	-	-	-
	GC: 11 W; 42 (32–55) yrs. BMI: n/m	430 (97) mmHg	-	-	-
Mengshoel *et al.* (1990) / Norway[23]	FM: 26 W; 43 (21-62) yrs. BMI: n/m Severity: n/m	58 (22) kPa	-	-	-
	GC: 26 W; n/m yrs. BMI: n/m	97 (17) kPa	-	-	-
Visuri *et al.* (1992) / Finland[24]	FM: 17 M; 20 (17–22) yrs. BMI: n/m Severity: n/m	27 (10) mmHg	-	-	-
	GC: 20 M; 21 (19–24) yrs. BMI: n/m	40 (13) mmHg	-	-	-
Verstappen *et al.* (1995) / Netherlands[15]	FM: 87 W; 45 (8.7) yrs. BMI: 25.8 (3.7) kg/m^2 Severity: n/m	64.4 (22.1) kPa	-	-	-
	GC: 52 W; 43.7 (6.5) yrs. BMI: 23.9 (3.2) kg/m^2	80.8 (15.4) kPa	-	-	-
Henriksson *et al.* (1996) / Sweden[25]	FM: 19 W; 36 (10) yrs. BMI: n/m Severity: n/m	251.1 (104) N	-	-	-
	GC: 40 W; 38 (10) yrs. BMI: n/m	406.1 (55.9) N	-	-	-
Lund *et al.* (2003) / Sweden[26]	FM: 9 W; 45 (34–52) yrs. BMI: n/m Severity: n/m	24.0 (22.0–50.0) N	-	-	-
	GC: 9 W; 45 (25–59) yrs. BMI: n/m	46.7 (32.2–51.5) N	-	-	-
Valkeinen *et al.* (2008) / Finland[43]	FM: 23 W; 58 (3) yrs. BMI: 27.4 (3.5) kg/m^2 Severity: n/m	343 (56.6) N	-	-	-

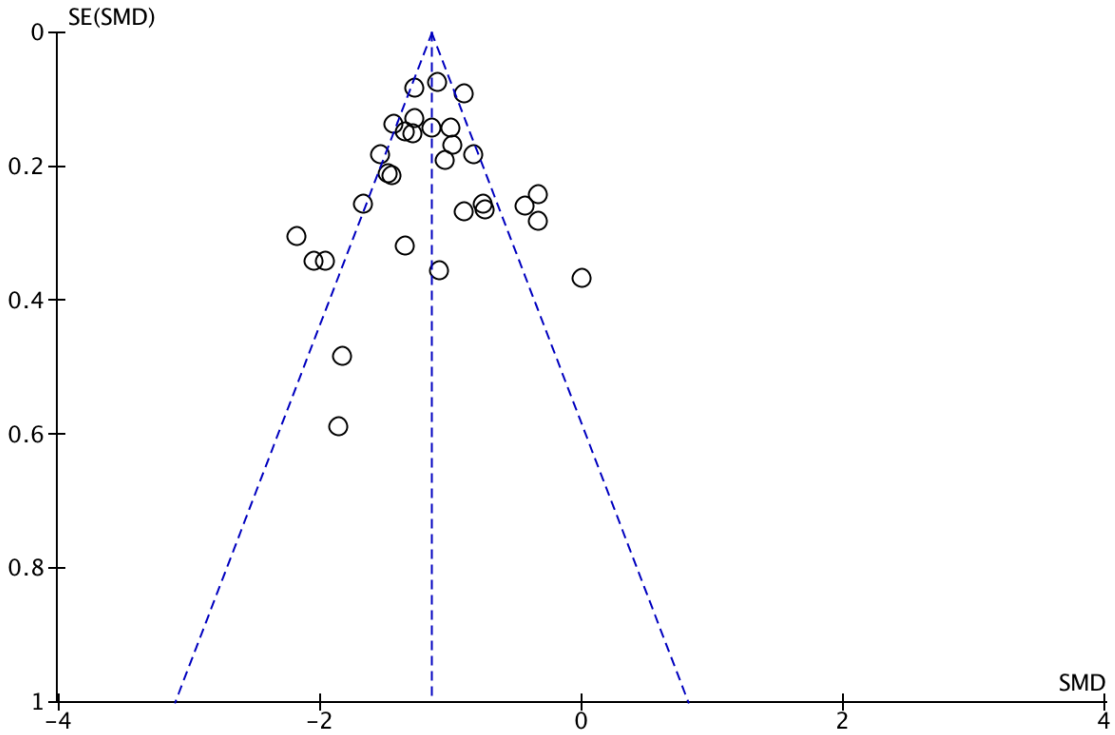
Aparicio *et al.* (2010) / Spain[36]	GC: 11 W; 58 (5) yrs. BMI: 25.6 (3) kg/m^2	343 (51.3) N	-	-	-
	FM: 20 M; 48 (8) yrs. BMI: 27.3 (2.8) kg/m^2 Severity: 74.7 (15.2) FIQ	32.9 (10.4) kg	-	-	-
	GC: 60 M; 49.5 (7.3) yrs. BMI: 26.8 (3.5) kg/m^2	39.8 (8.9) kg	-	-	-
Aparicio *et al.* (2011) / Spain[16]	FM: 81 W; 50 (7.4) yrs. BMI: 28.2 (5.2) kg/m^2 Severity: 67 (56–76) FIQ	19.3 (6.5) kg	-	-	-
	GC: 44 W; 47.7 (6.4) yrs. BMI: 27.4 (5.4) kg/m^2	27.9 (4.1) kg	-	-	-
Latorre-Roman *et al.* (2012) / Spain[37]	FM: 66 W; 52 (8) yrs. BMI: 28.2 (5.2) kg/m^2 Severity: 24W FIQ ≥ 70 pts; 42W FIQ < 70 pts.	FIQ ≥ 70: 22.4 (7.8) kg FIQ < 70: 25.8 (6.4) kg	-	-	-
	GC: 23 W; 50.3 (8.8) yrs. BMI: 28.1 (6) kg/m^2	26.8 (4.9) kg	-	-	-
Aparicio *et al.* (2013) / Spain[27]	FM: 94 W; 52 (8) yrs. BMI: 28.2 (0.6) kg/m^2 Severity: 66.4 (1.4) FIQ	17.5 (4.3) kg	-	-	-
	GC: 66 W; 53.8 (6) yrs. BMI: 30.2 (0.7) kg/m^2	25.3 (5.9) kg	-	-	-
Segura-Jiménez *et al.* (2015) / Spain[38]	FM: 566 W; 51.9 (8.3) yrs.; 24M; 47 (8.4) yrs. BMI: W: 28.6 (5.4) kg/m^2; M: 27.8 (4.6) kg/m^2 Severity: n/m	-	-	W: 22.8 (3.3) M: 31.7 (4.3)	-
	GC: 249 W; 49.3 (9.9) yrs.; 56M 49.7 (11.5) yrs. BMI: W: 26.6 (4.7) kg/m^2; M: 28.3 (3.9) kg/m^2	-	-	W: 23.0 (3.4) M: 33.1 (5.1)	-
Aparicio *et al.* (2015) / Spain[39]	FM: 487 W; 51.9 (8.3) yrs. BMI: 28.6 (5.4) kg/m^2 Severity: 64.5 (16.7) FIQR	19.7 (7.6) kg	-	22.7 (3.3)	-
	GC: 250 W; 49.3 (9.9) yrs. BMI: 26.5 (4.6) kg/m^2	29.6 (8.1) kg	-	23 (3.3)	-
Latorre-Román *et al.*	FM: 492 W; 30–69 yrs.	30–39yrs: 24.9 (8.3) kg	-	30–39yrs: 23.9 (4.6)	30–39yrs: 8.9 (1.4)

(2015) / Spain[40]	BMI: 26.3–29.7 kg/m^2 Severity: 66.0 (15.0) FIQ	40–49yrs: 20.7 (8.0) kg 50–59yrs: 18.7 (6.9) kg 60–69yrs: 17.8 (6.2) kg		40–49yrs: 23.7 (4) 50–59yrs: 22.8 (3.6) 60–69yrs: 21.8 (3)	40–49yrs: 9.3 (1.2) 50–59yrs: 9.1 (1.1) 60–69yrs: 9.1 (0.9)
	GC: 279 W; 30–69 yrs. BMI: 25.6–27.6 kg/m^2	30–39yrs: 30.8 (7.1) kg 40–49yrs: 29.8 (7.9) kg 50–59yrs: 28.8 (7.2) kg 60–69yrs: 28.9 (9.9) kg	-	30–39yrs: 25.8 (5.4) 40–49yrs: 25.3 (5.8) 50–59yrs: 24.2 (4.6) 60–69yrs: 24.7 (5.5)	30–39yrs: 9.4 (1.4) 40–49yrs: 9.4 (1.5) 50–59yrs: 9.4 (1.2) 60–69yrs: 9.5 (1.4)
Gómez-Cabello *et al.* (2015) / Spain[28]	FM: 28 W; 51.1 (8.4) yrs. BMI: 28.6 (6.5) kg/m^2 Severity: n/m	18.7 (5.9) kg	-	-	-
	GC: 22 W; 53.1 (7.4) yrs. BMI: 23.5 (28.6) kg/m^2	26.3 (5) kg	-	-	-
Álvarez-Gallardo *et al.* (2016) / Spain[29]	FM: 413 W; 52.3 (7.2) yrs. BMI: 28.6 (5.4) kg/m^2 Severity: n/m	Self-reported fitness Very poor: 17.2 (6.2) kg Poor: 19.3 (6.3) kg Average: 21.8 (5.9) kg Good: 20.5 (10.7) kg	-	-	-
	GC: 195 W; 51.3 (6.9) yrs. BMI: 26.7 (4.3) kg/m^2	Very poor: 23.4 (3.1) kg Poor: 23.6 (4.7) kg Average: 26.6 (4.3) kg Good: 29.1 (4.3) kg	-	-	-
Álvarez-Gallardo *et al.* (2017) / Spain[41]	FM: 468 W; 55.2 (8) yrs.; 21 M; 46.9 (8.4) yrs. BMI: W: 28.59 (5.4) kg/m^2; M: 28.1 (4.8) kg/m^2 Severity: n/m	W: 19 (6.5) kg M: 34.4 (13) kg	-	-	-
	GC: 360 W; 51.7 (8.2) yrs.; 55 M; 49.5 (11.2) yrs. BMI: W: 27.5 (4.8) kg/m^2; M: 28.2 (3.9) kg/m^2	W: 25.6 (5.2) kg M: 42.6 (6.9) kg	-	-	-
Castro-Piñero *et al.* (2017) / Spain[30]	FM: 492 W; 35–65 yrs. BMI: n/m Severity: 61.4–63.1 FIQR	35–44yrs: 21.7 (6.4) kg 45–54yrs: 19.6 (6.5) kg 55–65yrs: 18.9 (5.9) kg	-	-	-
	GC: 196 M; 35–65 yrs. BMI: n/m	35–44yrs: 27.8 (4.1) kg 45–54yrs: 27.3 (4.8) kg 55–65yrs: 24.5 (4.6) kg	-	-	-
Larsson *et al.* (2018) / Sweden[31]	FM: 118 W; 51.0 (9.5) yrs. BMI: 27.90 (5.28) kg/m^2	152.8 (65.3) N	-	-	-

Villafaina *et al.* (2018) / Spain[32]	Severity: 60.4 (15.6) FIQ GC: 93 W; 51.2 (9.6) yrs. BMI: 24.7 (3.5) kg/m^2	233.3 (56.9) N	-	-	-
	FM: 30 W; 55.3 (9.5) yrs. BMI: 27.1 (4.2) kg/m^2	24.1 (4.7) kg	-	-	-
	Severity: 48.8 (15.7) FIQ GC: 31 W; 50.8 (8.5) yrs. BMI: 24.7 (4.0) kg/m^2	25.9 (3.8) kg	-	-	-
Sempere-Rubio *et al.* (2019) / Spain[33]	FM: 123 W; 54.4 (6.8) yrs. BMI: n/m Severity: n/m	82.1 (56.9) kg	-	-	-
	GC: 100 W; 54.27 (6.1) yrs. BMI: n/m	155.2 (49.8) kg	-	-	-
Salaffi *et al.* (2020) / Italy[42]	FM: 110 W; 53.8 (12.4) yrs. BMI: 26.5 (2.2) kg/m^2 Severity: 52.6 (22.9) FIQR; 6.1 (2.3) FAS	14.8 (4.7) kg	-	-	-
	GC: 111 W; 55.2 (14.9) yrs. BMI: 25.9 (3.4) kg/m^2	19.9 (5.4) kg	-	-	-
Kapuczinski *et al.* (2022) / Belgium[34]	FM: 45 W; 48.9 (8.7) yrs. BMI: 26.2 (3.3) kg/m^2 Severity: 74 (13) FIQR	18 (8) kg	-	19.2 (2.7)	7.2 (0.5)
	GC: 39 W; 44.4 (7.3) yrs. BMI: 23.1 (3.5) kg/m^2	30 (6) Kg	-	19.6 (2.8)	7.4 (0.7)
Leon-Llamas *et al.* (2022) / Spain[35]	FM: 25 W; 56.4 (8.4) yrs. BMI: 26.79 (4.48) kg/m^2 Severity: 51.5 (17.8) FIQR	R: 24.5 (4.7) kg L: 23.0 (4.5) kg	-	-	-
	GC: 26 W; 54.7 (6.8) yrs. BMI: 24.7 (3.9) kg/m^2	R: 26.0 (3.9) kg L: 24.3 (3.9) kg	-	-	-
Vicente-Campos *et al.* (2023) / Spain[22]	FM: 35 W; 51.4 (7.5) yrs. BMI: 26.2 (5.3) kg/m^2 Severity: n/m	R: 16.4 (5.9) kg L: 16.3 (5.5) kg	-	23.1 (3.2)	-
	GC: 35 W; 53.1 (5.6) yrs. BMI: 23.8 (3.4) kg/m^2	R: 27.5 (4.1) kg L: 27.6 (4.1) kg	-	23.8 (2.5)	-

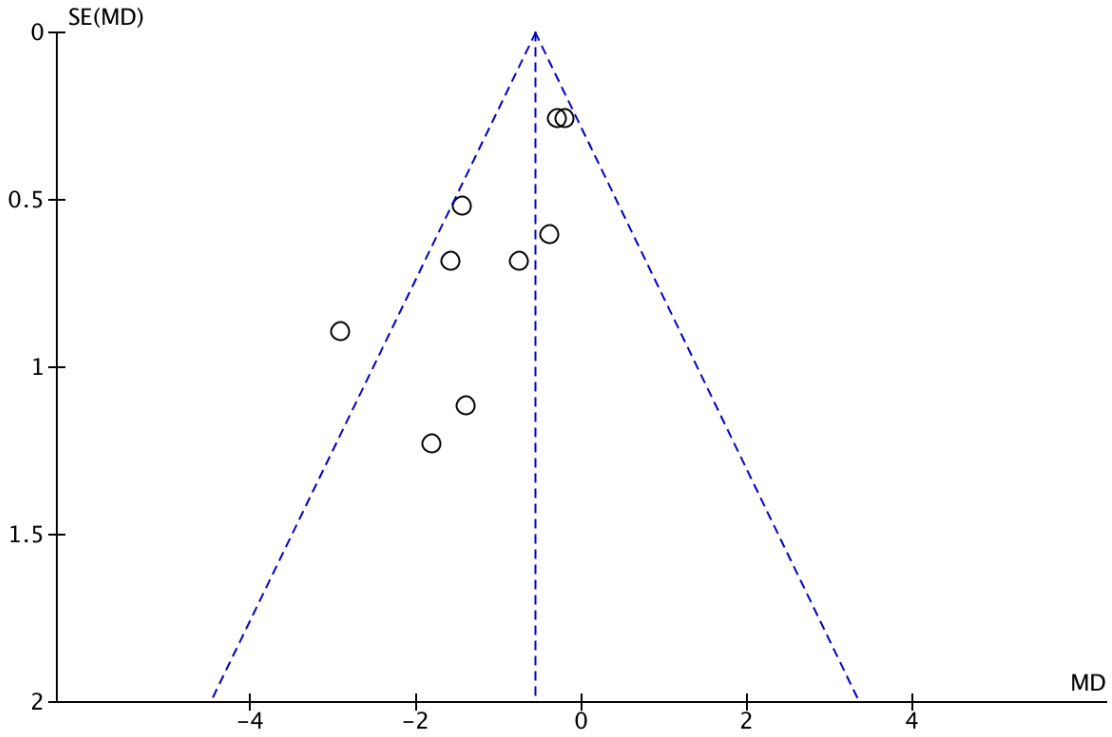
Data are reported as mean and standard deviation (SD) or median and range.
ASM: appendicular skeletal muscle; BMI: Body Mass Index; FAS: Fibromyalgia Assessment Status; FIQ: Fibromyalgia Impact Questionnaire; FM: fibromyalgia group; GC: control healthy group; L: left hand; n/m: not mentioned; R: right hand; SMI: Skeletal Muscle Index; W: women; 5STS: Five-Chair Stand Test.

SUPPLEMENTARY DIGITAL MATERIAL 4



Supplementary Figure 1.—Funnel plot of comparison: fibromyalgia *versus* healthy, outcome: handgrip strength.

SUPPLEMENTARY DIGITAL MATERIAL 5



Supplementary Figure 2.—Funnel plot of comparison: Fibromyalgia versus Healthy, outcome: Appendicular skeletal mass.

SUPPLEMENTARY DIGITAL MATERIAL 6

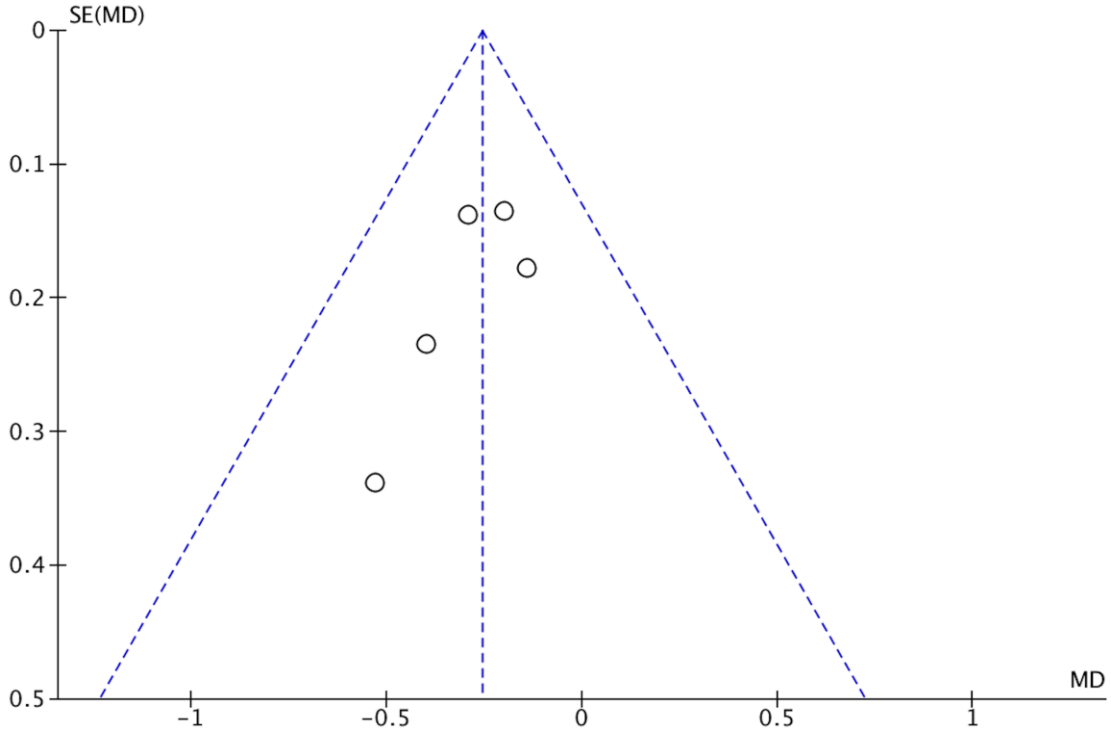
Supplementary Table I.—Certainty of the evidence with plain language summary. GRADE approach.

Outcome	Plain language statements	Absolute effect		Relative effect (95% CI)	Certainty of the evidence GRADE
		Fibromyalgia group	Healthy group		
Differences in muscle strength Handgrip strength (Kg) Assessed with: Handgrip dynamometer	The evidence suggests that European fibromyalgia individuals showed a large reduction in muscle strength compared to healthy individuals	-	- Average difference (SMD): 1.16 SD lower (95% CI: 1.29 to 1.03 SD lower) Based on data from 5461 individuals in 24 studies	-	⊕⊕⊕⊕ HIGH Due to serious risk of bias. Upgraded due to large magnitude of effect.
Differences in absolute muscle quantity ASM (Kg) Assessed with: Bioimpedance analysis	The evidence suggests that European fibromyalgia individuals may have a slightly reduction in absolute muscle quantity compared to healthy individuals	23.83 Kg	24.72 Kg Average difference (MD): 0.89 Kg lower (95% CI: 1.41 to 0.37 Kg lower) Based on data from 2537 individuals in 5 studies	-	⊕⊕◯◯ LOW Due to very serious risk of bias.
Differences in relative muscle quantity SMI (Kg/m^2) Assessed with: Bioimpedance analysis	The evidence suggests that European fibromyalgia individuals may have a slightly reduction in relative muscle quantity compared to healthy individuals	8.76 Kg/m^2	9.02 Kg/m^2 Average difference (MD): 0.26 Kg/m^2 lower (95% CI: 0.41 to 0.1 Kg/m^2 lower) Based on data from 839 individuals in 2 studies	-	⊕⊕◯◯ LOW Due to very serious risk of bias.
Risk of low muscle strength Handgrip strength (Kg) Assessed with: Handgrip dynamometer	The evidence suggests that European fibromyalgia individuals showed a large risk of probable sarcopenia (more than 9 times higher) compared to healthy individuals	322 per 1000 individuals	49 per 1000 individuals Difference: 273 more per 1000 individuals (95% CI: 213 to 343 more per 1000 individuals) Based on data from 5207 individuals in 20 studies	OR 9.23 (6.85 to 12.45)	⊕⊕⊕⊕ HIGH Due to serious risk of bias. Upgraded due to very large magnitude of effect.

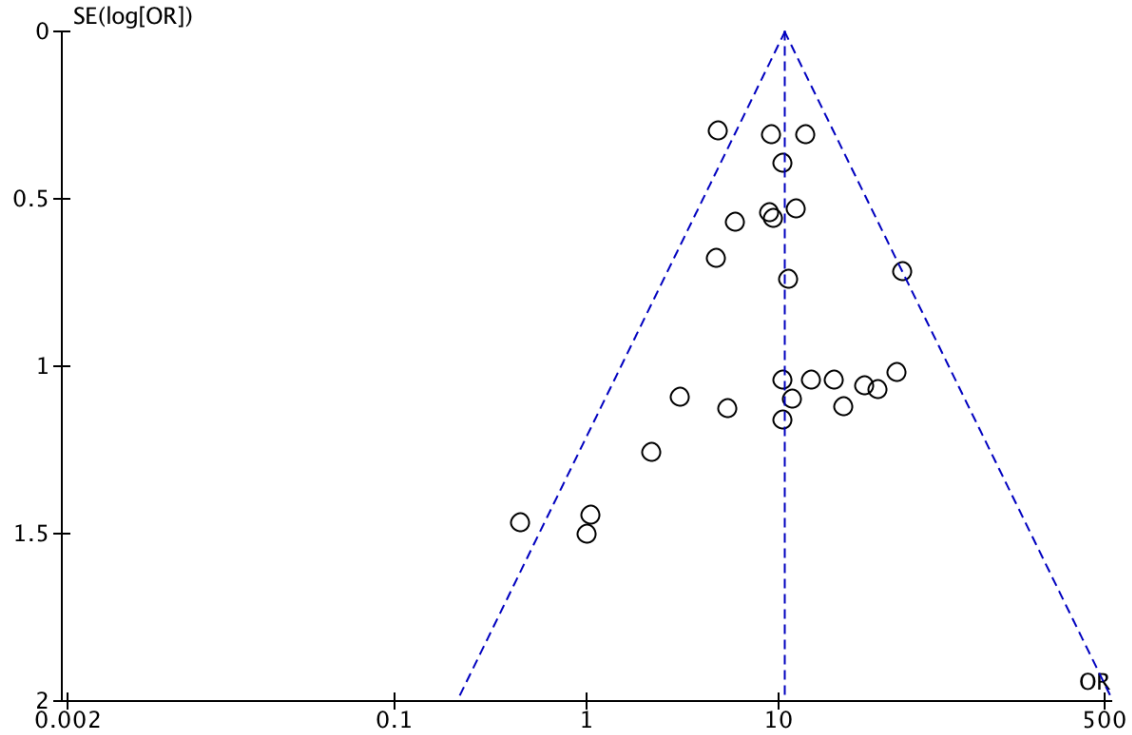
Risk of low absolute muscle quantity ASM (Kg) Assessed with: Bioimpedance analysis	The evidence suggests that European fibromyalgia individuals may have no difference in risk of reduced absolute muscle quantity compared to healthy individuals	19 per 1000 individuals 21 per 1000 individuals Difference: 2 fewer per 1000 individuals (95% CI: 11 fewer to 14 more per 1000 individuals) Based on data from 2537 individuals in 5 studies	OR 0.91 (0.49 to 1.67)	⊕⊕◯◯ LOW Due to very serious risk of bias.
Risk of low relative muscle quantity SMI (Kg) Assessed with: Bioimpedance analysis	The evidence suggests that European fibromyalgia individuals may have no difference in risk of reduced relative muscle quantity compared to healthy individuals	11 per 1000 individuals 16 per 1000 individuals Difference: 5 fewer per 1000 individuals (95% CI: 13 fewer to 21 more per 1000 individuals) Based on data from 839 individuals in 2 studies	OR 0.67 (0.19 to 2.33)	⊕⊕◯◯ LOW Due to very serious risk of bias.

95% CI: 95% confidence interval; ASM: appendicular skeletal mass; SMI: Skeletal Muscle Index.

SUPPLEMENTARY DIGITAL MATERIAL 7

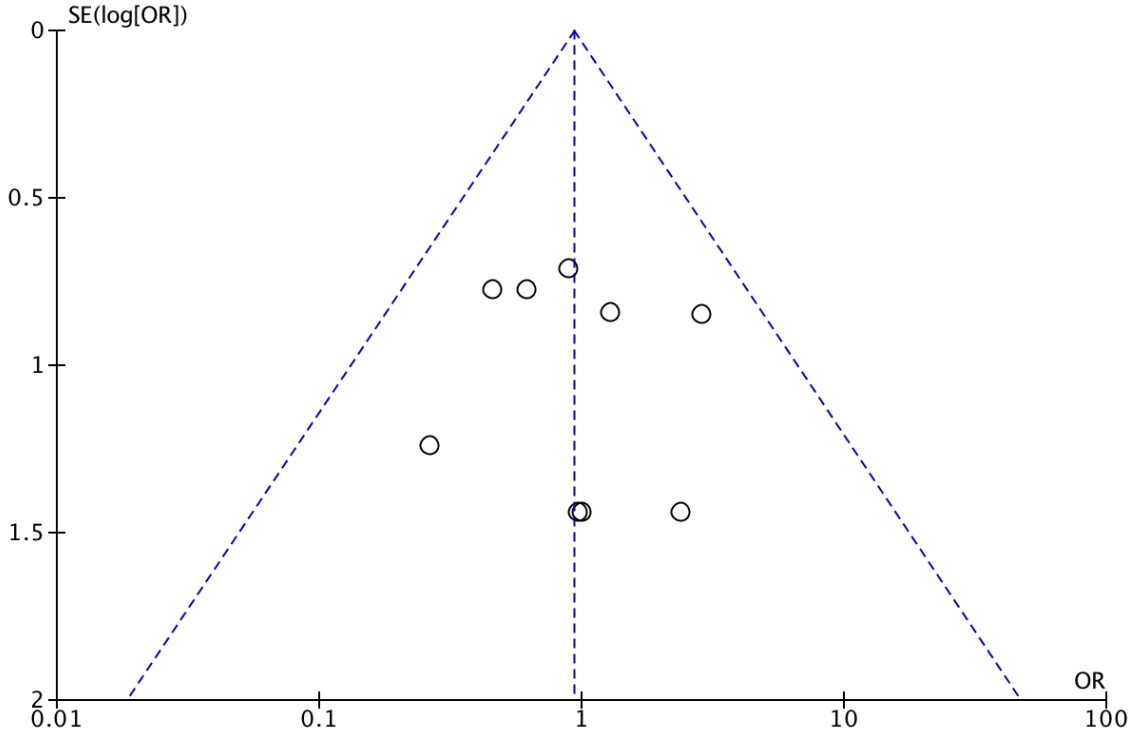


Supplementary Figure 3.—Funnel plot of comparison: fibromyalgia *versus* healthy, outcome: Skeletal Muscle Index.

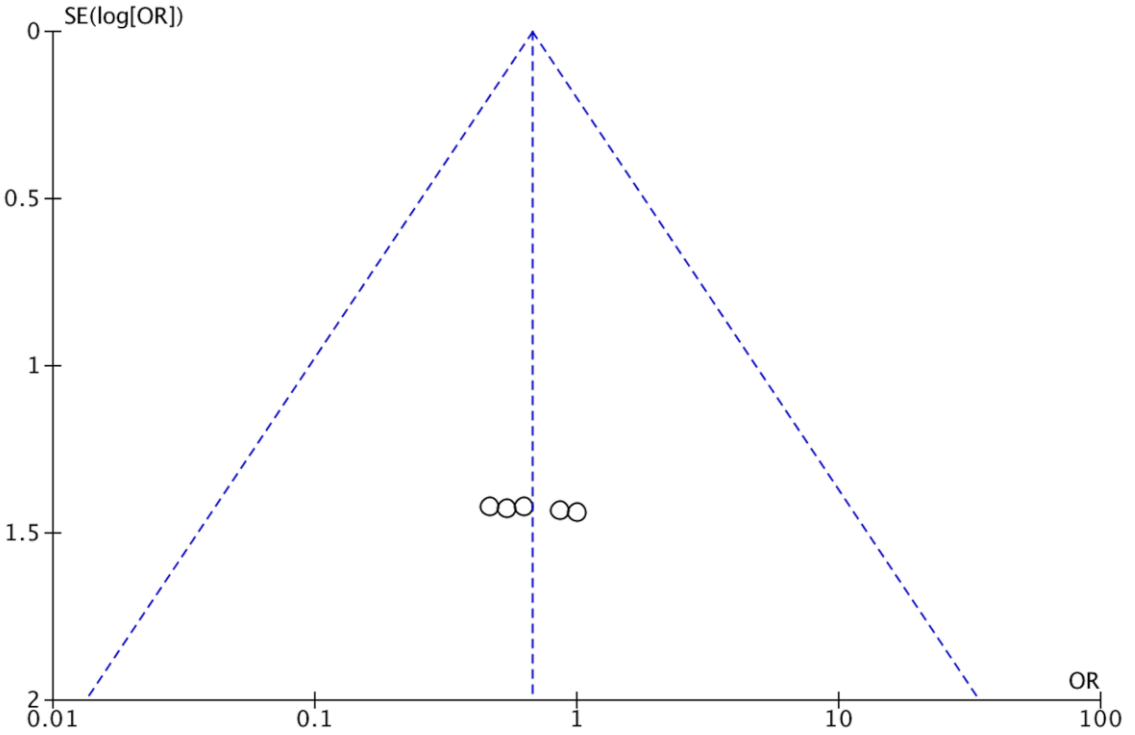


Supplementary Figure 4.—Funnel plot of comparison: Risk of reduced muscle strength, outcome: Handgrip strength cut-off point <27 kg in men and <16 kg in women.

SUPPLEMENTARY DIGITAL MATERIAL 8



Supplementary Figure 5.—Funnel plot of comparison: risk of reduced absolute muscle quantity, outcome: appendicular skeletal mass cut-off point <20 kg in men and <15 kg in women.



Supplementary Figure 6.—Funnel plot of comparison: risk of reduced relative muscle quantity, outcome: Skeletal Muscle Index cut-off point <5.5 kg/m^2 in women.