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Review article

Systematic review on the relationship between menopausal hormone replacement therapy, sarcopenia, and sarcopenia-related parameters

Marc F. Österdahl [a,b,*], Mary Ni Lochlainn [a,b], Carly Welch [a,b], Janice Rymer [c], Mark Ashworth [d], Julie Whitney [e,f], Emma L. Duncan [a,g], Claire J. Steves [a,b]

[a] Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, United Kingdom
[b] Department of Ageing and Health, Guy's & St Thomas NHS Foundation Trust, London SE1 7EH, United Kingdom
[c] Division of Women's Health, Kings College London, London SE1 7EH, United Kingdom
[d] Department of Population Health Sciences, King's College London, SE1 1UL, United Kingdom
[e] Academic Department of Physiotherapy, King's College London, London SE5 9RS, United Kingdom
[f] King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom
[g] Department of Diabetes and Endocrinology, Guy's & St Thomas NHS Foundation Trust, London SE1 7EH, United Kingdom

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ABSTRACT

Objective: Whilst the beneficial effect of menopausal hormone replacement therapy (HRT) on osteoporosis is well established, its effect on sarcopenia is less clear. We conducted a systematic review of evidence exploring the relationship between HRT and sarcopenia.

Methods: We searched OVID Medline, Embase, CINAHL and Web of Science to 8 August 2024, identifying both in randomised controlled trials (RCTs) and observational studies of community-dwelling women. We excluded articles focussed on androgen therapy, or hormone therapy for indications other than menopause.

Our primary outcome was the effect of HRT upon sarcopenia defined by a consensus set of criteria (e.g. the definition proposed by the European Working Group on Sarcopenia in Older People 2). Grip strength, measures of physical performance, and radiological measures of muscle quantity were included as secondary outcomes. Reporting follows PRISMA guidelines.

Results: Searches identified 6090 articles, of which 43 were included in our final analysis. No studies used a consensus definition of sarcopenia. Most used data over 20 years old, with older formulations of HRT, though formulations were inconsistently reported.

Of the 15 RCTs included, two of six suggested a beneficial effect on grip strength, one of six on physical performance, and seven of 12 on radiologically assessed muscle quantity.

Of the 28 observational studies included, three of 11 suggested a beneficial effect on grip strength, two of seven on physical performance and three of 18 on radiologically assessed muscle quantity.

No studies reported detrimental effects on muscle. Risk of bias was high/severe. Observational models seldom adjusted for confounders.

Conclusions: No studies used modern consensus definitions of sarcopenia. For secondary outcomes, there was no consistent evidence of benefit, with methodological flaws, and outmoded HRT formulations.

Abbreviations: ALM, appendicular lean mass; ANOVA, analysis of variance; ASM, appendicular skeletal muscle mass; BMD, bone mineral density; BMI, body mass index; CEE, conjugated equine oestrogens; CPA, cyproterone acetate; CT, Computerised Tomography; DXA, dual X-ray absorptiometry; E2, estradiol; GS, grip strength; HRT, menopausal hormone replacement therapy; m/s, meters per second; MPA, medroxyprogesterone acetate; MRI, Magnetic Resonance Imaging; PRISMA -, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomised controlled trial; RoB2, Cochrane Risk of Bias tool version 2; ROBINS-I, Cochrane Risk Of Bias In Non-randomised Studies of Interventions tool; sd, standard deviation; Tib, tibolone; UK, United Kingdom; USA, United States of America; WHI, Women's Health Initiative Trial.

* Corresponding author at: Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, United Kingdom.
E-mail addresses: marc.osterdahl@kcl.ac.uk (M.F. Österdahl), mary.ni_lochlainn@kcl.ac.uk (M. Ni Lochlainn), carly.welch@kcl.ac.uk (C. Welch), Janice.rymer@kcl.ac.uk (J. Rymer), Julie.whitney@kcl.ac.uk (J. Whitney), emma.duncan@kcl.ac.uk (E.L. Duncan), claire.j.steves@kcl.ac.uk (C.J. Steves).

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1. Introduction

Sarcopenia is a pathological decline in muscle mass, strength, and performance. It is increasingly common with older age [1] and linked to multiple adverse outcomes, particularly falls, fractures, the need for assistance with activities of daily living, a lower quality of life, and increased mortality [2,3]. It is influenced by genetic factors, long-term conditions, physical activity, nutrition, and other individual environmental factors. Sarcopenia is also a key contributor to frailty, the loss of physiological resilience associated with ageing, which is twice as common in older women as older men [4,5].

Androgens (e.g., testosterone) are well known to have anabolic effects on muscle in both men and women [6]. However, oestrogen may also have anabolic effects, in both sexes. Muscle tissue has also been shown in both animal models and humans to express oestrogen receptors, and oestradiol (E2) stimulates muscle regeneration, and the proliferation of satellite cells. E2 levels have been observed in cross-sectional studies to correlate with muscle strength and mass, and muscle growth or involution may respond to changes in oestrogen levels [6–8].

The menopause transition is clinically defined as cessation of menses for over 12 months, and biologically characterised by a substantial decline in oestrogen (and progesterone) levels [9]. Loss of oestrogen is known to increase bone turnover and reduces bone mineral density (BMD); and menopausal hormone replacement therapy (HRT) ameliorates these processes [10,11].

Menopausal decline in oestrogen may also accelerate muscle loss in women, with evidence of increased lipid infiltration, decreased type II fibres and fewer fast motor units [7,12]. Premature ovarian insufficiency or early menopause (<45 years), whether surgical or spontaneous, is associated with reduced later life grip strength [13–15], increased osteosarcopenia [15–17], more functional limitation [18] and greater multimorbidity [19]. HRT is often recommended for these women, particularly for its benefit on bone and blood pressure [9]. Similar muscle changes also occur in women experiencing menopause in the normal age range (45-55 years). However, the effect of HRT on sarcopenia in either group is unclear, with conflicting results from previous studies [20].

The aim of our systematic review is to explore existing evidence regarding HRT and sarcopenia in community-dwelling women, seeking to understand discrepancies between previous studies, in the context of the sex imbalance in age-related frailty.

2. Methods

2.1. Study design

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. It was pre-registered with PROSPERO (Prospective Register of Systematic Reviews - CRD42023441245).

2.2. Inclusion & exclusion criteria

We included both randomised controlled trials (RCTs) and observational studies of community-dwelling women, which compared the use of HRT with either placebo, or with no use of HRT (Fig. 1). We did not place age restrictions on the women included in studies but did exclude studies where enrolment was primarily based on another diagnosis or intervention, e.g.: women post-chemotherapy, or women with Turner's syndrome.

We defined HRT to include supplementation with oestrogen alone, oestrogen and progestogen/progesterone, or tibolone. Androgen supplementation is not recommended for peri-menopausal women, other than for low libido continuing after HRT initiation, so studies focused on androgens were excluded. Phyto-oestrogens and "compounded bio-identical hormones" were also excluded.

Population	Peri- or Post-menopausal cis-gender Women
Intervention	Menopausal hormone replacement therapy containing oestrogen +/- progestogen, or tibolone
Comparison	Women not taking any form of sex hormone
Outcomes	a. Sarcopenia as assessed by a consensus definition b. Grip Strength c. Gait Speed and physical performance d. Muscle quantity/mass assessed radiologically

Fig. 1. PICO criteria.

Our primary outcome of interest was any consensus definition of sarcopenia, as these are now considered to be the best measures for use in research and clinical practice [3]. There are currently several regional variations (e.g., European Working Group on Sarcopenia in Older People 2 definition), partly due to differences in body composition measures by ethnicity in different populations [2]. Most definitions include a measure of muscle strength, physical performance, and muscle quantity, requiring at least two components to be deficient for a diagnosis of sarcopenia. However, as most consensus definitions were only developed in the past 15 years, we included grip strength, physical performance, and radiological assessment of muscle quantity as three secondary outcomes, allowing a) inclusion of older studies and b) inclusion of these specific components from studies that were not fully comprehensive in their assessment of sarcopenia (Fig. 1).

2.3. Search strategy & study selection

We searched OVID Medline, Embase, CINAHL and Web of Science from inception to 8 August 2023, without language restriction. Full search terms and strategies for all databases are included in supplementary materials (Appendix B- Search Strategies). Results were imported to Endnote and Rayyan.ai. Title and abstracts were screened by MFÖ with a 25 % random sample rescreened by MNL. All full texts were reviewed by MFÖ and MNL; text references were also reviewed to capture all pertinent studies. Disagreements were resolved at both stages by consensus. Searches were repeated to 8 August 2024, following the same procedure. No large-language model or other 'artificial intelligence' screening was used.

2.4. Data extraction

Data were extracted by MFÖ according to what was reported in each study. Baseline demographics included biological variables (age, body mass index [BMI], age at menarche, age at menopause), socio-demographic variables (ethnicity/race, income, education, deprivation), lifestyle factors (smoking, alcohol, physical activity).Results pertaining to sarcopenia were extracted (e.g.: grip strength [in kg], lean body mass [in kg]), with note made of whether adjustment was performed for confounding variables, and whether the relationship between sarcopenia and HRT was the primary interest of the study.

2.5. Risk of bias

Risk of bias was assessed in RCTs using the Cochrane RoB2 tool and in observational studies using the ROBINS-I tool (v1) [21].

2.6. Synthesis and presentation of results

Included articles were split into RCTs and non-randomised/observational studies. Some studies reported themselves as trials, but without randomisation (e.g.: HRT use by patient choice); these were grouped with other observational (cohort) studies.

Initially, we hoped to perform meta-analysis of the RCTs. To this end, we recalculated results as needed to provide standardised mean differences and standard deviations; and assessed heterogeneity (using I^2), comparability of methods for reporting outcome measures, and study characteristics (including size, age, and geographical location). Heterogeneity was extremely high (e.g., $I^2 > 90$ % for grip strength and radiological measurements of sarcopenia) with wide variation in study size and participant ages and other characteristics. Therefore, we concluded that meta-analysis would be inappropriate. Similarly, funnel plots to assess for publication bias were not constructed due to the same considerations.

Therefore, results were synthesised and are presented narratively, acknowledging underlying differences between studies and discussing the uncertainty of results. Although study types are predominantly discussed separately, narrative comparisons are also made between RCTs and observational studies.

3. Results

3.1. Study selection

Database searches initially identified 5603 articles; 1519 were removed as duplicates. Abstracts of 4084 articles were screened by MFÖ and MNL; decisions regarding inclusion/exclusion were concordant for 97 % of articles. Discordant categorisation was solved by discussion without need for a third reviewer. 79 articles underwent full text review for inclusion/exclusion, with any disagreement again resolved by consensus: 37 were excluded (13 were studies where the cohort was presented in another article more suitable for inclusion; 14 studies did not explicitly identify the effect of HRT; and 10 studies did not report an appropriate outcome of interest) (Fig. 2).

Further searches through references revealed one further article for inclusion. Additional searches to 8 August 2024 revealed a further 487 articles, reduced to 433 after deduplication. Only one was suitable for full text review, after title & abstract screening, and was subsequently included, but replacing one observational study on the same cohort from the original search, finally resulting in 43 articles for this review: 15 RCTs and 28 non-randomised observational studies (Fig. 2).

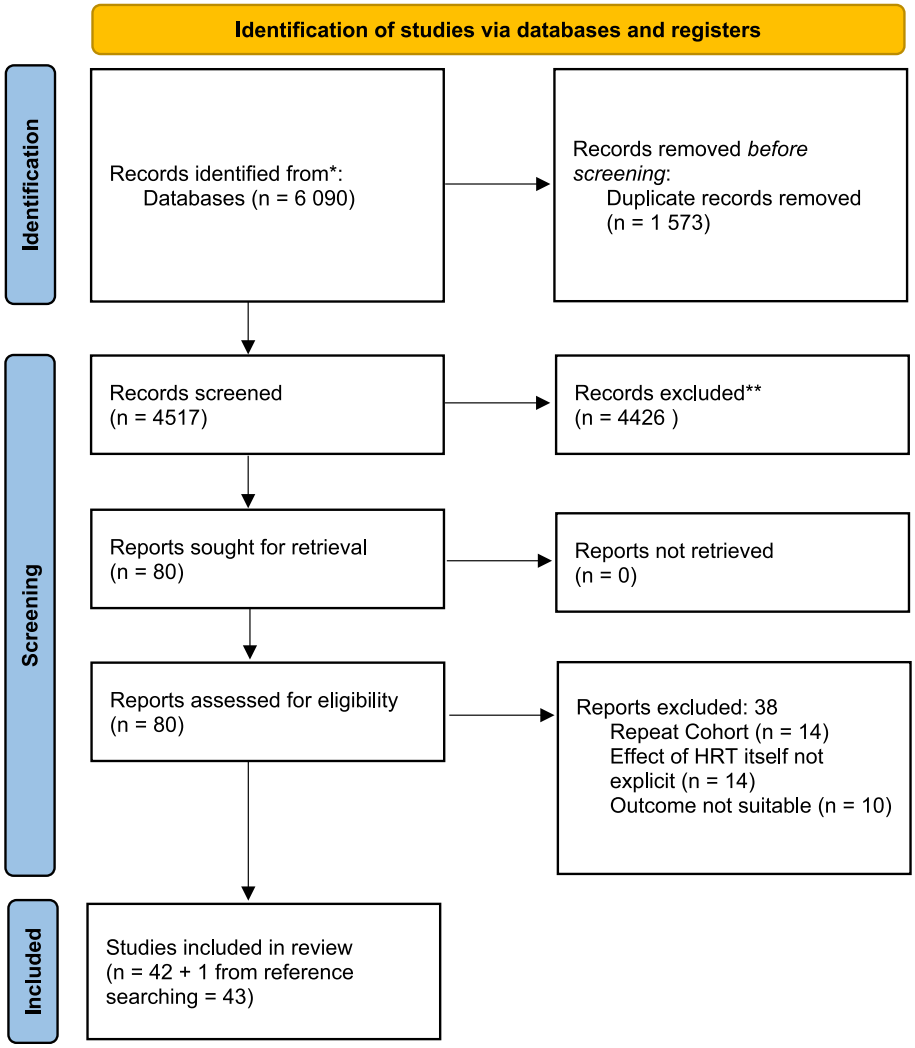

Fig. 2. PRISMA diagram: Flowchart of the assessment of articles for inclusion in systematic review.

3.2. Study characteristics

3.2.1. Randomised controlled trials

Fifteen articles reporting results from RCTs were identified for this review. Of these, seven were initiated before 2000; six had unclear start and end dates; six were published after 2010. All were from North America and Western Europe, most commonly from United States of America (USA) (n = 5) (Supplementary Table A1). Only two articles included over 500 participants, both secondary analyses of data from the Women's Health Initiative (WHI) trial, though assessing different outcomes [22,23]. Ten included fewer than 100 participants [24–33] (Tables 1–3).

Ages of participants varied substantially across studies. Average age at enrolment was <60 years in seven articles [25–30,32], and > 70 years in four articles [24,34–36] (Tables 1–3). Average BMI was in the overweight (25-29.9 kg/m^2) range for most (11 of 15) articles, noting that some also excluded women with extreme BMI or weight. Only three articles, all from the USA, reported information on ethnicity or race: two WHI studies, with 78 % and 88 % participants classified as non-Hispanic white [22,23], and one including 64 % non-Hispanic white participants [34].

There was significant variation on the formulations of HRT used. With respect to oestrogen: three used oral conjugated equine oestrogens (CEE – Premarin) [22,23,36], common in the 1990s but now less favoured, five used oral oestradiol [26,28–30,34], and four used transdermal oestradiol (either gel or patches) [24–26,31], now often preferred due to its safety profile [9]. With respect to progestogens: six used medroxyprogesterone acetate (MPA) [22–25,33,36], whilst only one used micronized progesterone [34], now commonly used. Tibolone was used in 5 studies, but at two different daily doses (three: 2.5 mg [26,27,32]; two 1.25 mg (considered a reduced dose) [31,35]). Some articles include multiple arms of HRT with different preparations (Tables 1–3).

3.2.2. Observational

We identified 28 observational studies for this review. Many of these were published nearly two decades ago: seven before 2000 [37–43], with a further nine from 2000 to 2005 [14,44–51] (Tables 4–6).

As with RCTs, most were from North America (14 from the USA) and Europe (12 studies) with one each from Brazil [52] and South Korea [53] (Supplementary Table A2). Fourteen had fewer than 100 participants [39,40,45,46,48–52,54–58]; four had over 5000 women [41,59–61]. Seven reported longitudinal follow-up of their cohort [14,40,43–46,60], though only two were longer than 12 months [14,60]. Thirteen were purely cross-sectional; eight were from longitudinal cohorts but only analysed data from a single timepoint (Tables 4–6).

Age again varied substantially: younger than 60 years in 19 studies, older than 70 years in three studies (Tables 4–6). Half (14 studies) included articles reported an average BMI that was overweight (25-29.9 kg/m2), whilst eight did not report BMI. Only five describe ethnicity or race, all with predominantly white non-Hispanic women. Of note, one study excluded black women [41].

Type of HRT was poorly described. Twelve assessed HRT without specifying any further details on formulation. Ten specified oestrogen with or without a progestogen, and five were unclear regarding progestogen use. Only two studies had explicitly reported tibolone use, one with only 4 users [55].

3.3. Risk of Bias assessment

Using the Cochrane RoB2 tool, 22 assessments were made on fifteen RCT articles, accounting for some articles where multiple outcomes are reported, with potential for differential risks of bias in each outcome. Of these 22, four have a high risk of bias, most (15/22) display some concerns (most commonly for poor documentation of randomisation and pre-specified analysis plan) and three were deemed low risk (Supplementary Table A1).

The ROBINS-I tool was used for observational studies, with all 40 assessments demonstrating at least serious risk of bias overall, and seven critical risk. Only 1 study reported sufficient information on adherence to be determined "Low" risk of bias for this domain, whilst 3 were likely critical (Supplementary Table A2). 18 articles reported results using methods unable to control for confounding variables (e.g.: analysis of variance – ANOVA – Appendix D – Supplementary Table D1).

3.4. Outcomes

3.4.1. Consensus definition

None of the articles assessed used a consensus definition of sarcopenia.

3.4.2. Grip strength

This was reported in six RCTs and 11 observational studies:

RCT data: two demonstrated an improvement in grip strength [25,32], whilst four show no difference. Of the two studies showing benefit: both were of younger participants (mean age < 60): one assessing 2.5 mg tibolone vs. placebo [32], and one transdermal oestradiol + MPA vs. placebo [25] (Table 1).

Observational data: three articles demonstrated higher grip strength amongst HRT users [38,47,52]. The remaining eight found no difference (Table 4).

Table 1
Randomised controlled trials assessing the association between the use of menopausal hormone replacement therapy and grip strength.

Grip strength						
First author	Year	N	Age (years) – Mean (sd)	Formulation	Duration	Result
Dam, T [25]	2021	31	54 (3.9)	Transdermal oestradiol patch with 10 mg MPA after intervention for 10 days	12 weeks	Improvement with HRT (28.3 kg to 30.0 kg: +1.7 kg, p < 0.01, no 95 % CI reported)
Jacobsen, D [35]	2012	189	74 (3.3)	Tibolone 1.25 mg	Up to 24 months	No difference
Meeuwsen, I [32]	2002	85	54 (4.6)	Tibolone 2.5 mg	1 year	Greater with HRT (26.77 kg to 27.76 kg: +0.99 kg – 95 % CI [0.06-1.93 kg])
Michael, Y [23]	2010	2380	Age range: 65-69: 50 % 70-79: 50 %	CEE with 2.5 mg MPA or CEE alone	6 Years	No difference
Ribom, E [31]	2011	80	68 (5.1)	Tibolone 1.25 mg	24 weeks	No difference
Ribom, E [33]	2002	40	67 (1.0)	Transdermal oestradiol patch with 2.5 mg MPA daily during intervention	6 Months	No difference

sd – standard deviation, MPA – medroxyprogesterone acetate, CEE – conjugated equine oestrogen, HRT – menopausal hormone replacement therapy, 95 % CI – 95 % confidence interval.
Michael et al. have reported only distribution of age ranges, without a mean/sd for the cohort or subgroups.

Table 2
Randomised controlled trials assessing the association between menopausal hormone replacement therapy and measures of physical performance.

Physical performance								
First author	Year	N	Age (years) – Mean (sd)	Formulation	Duration	Walking speed	Vertical jump height	Chair stands/rising time
Dam, T [25]	2021	31	54 (3.9)	Transdermal oestradiol patch with 10 mg MPA after intervention for 10 days	12 weeks	6 min walk - no improvement	Countermovement jump - no difference	Sit to stand - placebo performed better than intervention with exercise
Greenspan, S [36]	2005	373	71 (5.2)	CEE + MPA or CEE	3 years	15 ft. walk - No difference	–	No difference
Kenny, A [34]	2005	167	74 (0.7)	Oral oestradiol with micronized progesterone	3 years	8 ft. walk - No difference	–	No difference
Michael, Y [23]	2010	2380	Age range: 65-69: 50 % 70-79: 50 %	CEE + MPA or CEE	6 years	6 m walk - No difference	–	No difference
Ribom, E [31]	2011	80	68 (5.1)	Tibolone 1.25 mg	24 weeks	–	–	Equal improvement in placebo and intervention
Taaffe, D [30]	2005	80	Age Range: 50-57	Oral oestradiol with norethisterone	1 year	Running speed Improved with HRT (4.9 m/s to 5.1 m/s, p = 0.035)	Improved with HRT (15.2 cm to 16.2 cm, p = 0.043)	–

sd – standard deviation, MPA – medroxyprogesterone acetate, CEE – conjugated equine oestrogens HRT – menopausal hormone replacement therapy.
Michael et al and Taaffe et al. have reported only distribution of age ranges, without a mean/sd for the cohort or subgroups.

Table 3
Randomised controlled trials assessing the relationship between menopausal hormone replacement therapy and radiological measures of sarcopenia.

Radiological assessment						
First author	Year	N	Age (years) – Mean (sd)	Formulation	Duration	Result
Dual X-ray absorptiometry						
Bea, J [22]	2011	1941	63 (7.4)	CEE with 2.5 mg MPA or CEE alone	6 years	No difference
Blackman, M [24]	2002	28	72 (1.2)	Oestradiol patch (110 μg/24 h) with 10 mg MPA for last 10 days of each cycle	6 months	No difference
Dam, T [25]	2021	31	54 (3.9)	Oestradiol patch (100 μg/24 h) with 10 mg MPA after intervention for 10 days	12 weeks	Increase in Fat-Free Mass with HRT (HRT +5.5 % vs Plc +2.9 %, p < 0.05)
Hänggi, W [26]	1998	HRT: 26 Plc: 26	52 (2.8)	Micronized oestradiol (2 mg/day) with 10 mg dydrogesterone for 14/28 days	2 years	No difference compared to placebo.
Hänggi, W [26]	1998	HRT: 20 Plc: 26	52 (2.7)	Oestradiol patch (50 μg/day) with 10 mg dydrogesterone for 14/28 days	2 years	Less/No deterioration in total body lean mass with transdermal HRT (HRT +0.3 kg [sd 0.8], Plc -1.7 kg [sd 0.7])
Hänggi, W [26]	1998	Tib: 28 Plc: 26	53 (3.0)	Tibolone 2.5 mg	2 years	Less/No deterioration in total body lean mass with HRT (TIB: +0.4 kg [sd 0.5], Plc: −1.7 kg [sd 0.7])
Jacobsen, D [35]	2012	189	74 (3.3)	Tibolone 1.25 mg	2 years	Increase in Fat-Free Mass with HRT only (40.7 kg to 42.0 kg: +1.3 kg, 95 % CI [0.5–2.0 kg])
Kenny, A [34]	2005	167	74 (0.7)	Oestradiol (0.25 mg/day) with micronized progesterone 100 mg/day for 2 weeks every 6 months	3 years	No difference
Sørensen, M [28]	2001	16 - crossover	56 (2.6)	Oestradiol 4 mg for 22 days, then 1 mg for 6 days, with norethisterone 1 mg for 10 days	9 months	Less deterioration/increase in lean body mass with HRT (HRT: +0.347 kg [sd 0.85], Plc –0.996 kg [sd 1.58] p < 0.05)
Tanko, L [29]	2021	51 (2.0)	51 (2.0)	Oestradiol 2 mg with CPA 1 mg daily	3 years	No difference with HRT
Tanko, L [29]	2021	50 (2.0)	51 (2.0)	Oestradiol 2 mg with levonorgestrel 75μg for 12 days	3 years	No difference with HRT
Tommaselli, G [27]	2006	50	49 (4.0)	Tibolone 2.5 mg	1 year	Increased total and lean mass with HRT
Cross sectional imaging						
Dam, T [25]	2021	31	54 (3.9)	Oestradiol patch (110 μg/24 h) with 10 mg MPA for last 10 days of each cycle	12 weeks	By MRI: Increased muscle area with HRT in one region only (HRT +7.4 %, Plc +3.9 %, p < 0.05)
Taaffe, D [30]	2005	80	Age range: 50-57	Oestradiol 2 mg with Norethisterone 1 mg daily	1 year	By CT: Increased quadriceps + posterior thigh muscle area with HRT (Quad: 44.9 cm to 47.5 cm, p < 0.001, posterior thigh: 44.3 cm to 47.3 cm, p = 0.02)

sd – standard deviation, Tib – tibolone, Plc – placebo, MPA – medroxyprogesterone acetate, CEE – conjugated equine oestrogens CPA – cyproterone acetate, HRT – menopausal hormone replacement therapy.
Taaffe et al. have reported only distribution of age ranges, without a mean/sd for the cohort or subgroups.

3.4.3. Physical performance

This was reported in six RCTs and seven observational studies:

RCT data: Five reported gait speed; of these, one showed improvement with HRT, measuring running speed [30]. Two studies reported vertical jump height, one of which demonstrating improvement after 1 year of HRT [30]. Five studies reported chair rise time, none

Table 4
Observational studies assessing the association between the use of menopausal hormone replacement therapy and grip strength.

Grip Strength					
First Author	Year	N	Age (years) – Mean (sd)	Result	Length of follow-up & notes
Longitudinal Cohort					
Greeves, J P [40]	1999	21	51 (3.6)	No difference (decline in both groups)	39 Weeks follow-up
Kurina, L [14]	2004	563	46 (2.8)	Overall no difference but African-American HRT users reported to have increased grip strength (numerical result not shown)	3 years follow-up
Cross sectional					
Barbat-Artigas, S [54]	2010	46	62 (6.4)	No difference	
Bassey, EJ [37]	1995	229	49 (3.1)	No difference	
Bemben, DA [50]	2002	40	59 (5.6)	No difference	
Cauley, J [38]	1987	310	57 (4.5)	GS higher with HRT (27.47 kg vs 25.30 kg, $p < 0.05$)	
Cooper, R [62]	2008	1386	53 (not given)	No difference	
Costa, G [52]	2011	50	53 (4.7)	GS higher with HRT (26.61 kg vs 23.75 kg, $p < 0.05$)	
Macedo, P [61]	2024	12,506	63 (10.0)	No difference	
Preisinger, E [39]	1995	61	60 (1.4)	No difference	
Taaffe, D [47]	2005	840	74 (2.8)	GS higher with HRT (both hands – 45.6 kg vs 44.1 kg, $p = 0.022$)	

GS = Grip Strength, HRT – menopausal hormone replacement therapy.

Table 5
Observational studies assessing the association between the use of menopausal hormone replacement therapy and physical performance.

Physical Performance					
First Author	Year	N	Age (years) – mean (sd)	Result	Length of follow-up & notes
Longitudinal Cohort					
Forrest, KYZ [60]	2006	5178	70 (4.2)	Walking Speed - decline greater in HRT users Chair stands - No difference	10 years follow-up
Cross sectional					
Cooper, R [62]	2008	1386	53 (not given)	Chair Rise - No difference Standing Balance - No difference	
Le Noan-Lainé, M [59]	2023	33,892	57.2 (0.0)	Walking speed - No difference	
Macedo, P [61]	2024	12,506	63 (10.0)	Walking Speed (m/s)– higher in HRT users (β = 0.01 95 % CI 0.00 to 0.02) Timed up and go test (seconds) – faster in HRT users (β = −0.22, 95%CI -0.30 to −0.13) Chair rise – no difference Balance test – no difference	
Ronkainen, P [55]	2009	30	57.2 (1.8)	Habitual walking speed - no difference Maximal walking speed - Higher in HRT users (2.2 m/s vs 2.0 m/s)	
Seeley, D [41]	1995	9704	71 (4.6)	Walking speed - No difference	
Taaffe, D [47]	2005	840	74 (2.8)	Chair stands - No difference 6 m walk - No difference Standing balance - No difference	

HRT – menopausal hormone replacement therapy. m/s – metres per second. 95 % CI – 95 % Confidence Interval.

demonstrating any improvement after HRT (Table 2).

Observational data: one cross-sectional study reported faster maximal walking speed in HRT users [55]; one cross-sectional study reported higher walking speed and faster timed up and go results in HRT users, after adjustment for confounding [61]. However, one longitudinal study reported greater decline during follow-up habitual walking speed in HRT users [60]. No other measures of physical performance (chair rise, standing balance, 6 m walk) were associated with HRT use (Table 5).

3.4.4. Radiological assessment

This was assessed in 14 RCTs and 18 observational studies, using Computerised Tomography (CT), Magnetic Resonance Imaging (MRI) and dual-energy x-ray absorptiometry (DXA).

RCT data: Two studies used cross-sectional imaging: one, using CT, showed improvement in muscle mass with HRT [30]; one, using MRI, showed improvement in muscle mass in some regions but not all [25].

Twelve studies reported DXA measurements: four showed increased muscle mass/quantity after HRT use [25,27,28,35]; one study, using with three different formulations of HRT, showed 'less decline' longitudinally compared to control [26]; and four studies showed no difference [22,24,29,34] (Table 3).

Observational data: 17 articles were identified – two, using CT, showed greater muscle mass for HRT users in some areas, but not necessarily all [47,55]. 15 used DXA, with one showing greater appendicular skeletal muscle mass (ASM) in HRT users [52], one reporting lower odds of low ASM/weight [53], and the remainder demonstrating no difference. No studies used MRI (Table 6).

3.5. Sensitivity analyses

3.5.1. Women over 65 at assessment of outcome

RCT data: Four articles on grip strength had an average age > 65 years, but none showed an improvement with HRT [23,31,33,35]. Four articles on physical performance have an average age > 65 years [23,31,34,36], with none showing an improvement. Three trials examining radiological measures of muscle mass had average ages >65 years [24,34,35], with one showing an increase in fat-free mass [35].

Observational data: One study performed a stratified analysis of participants above or below 65 years, showing benefit in physical

Table 6
Observational studies assessing the association between the use of menopausal hormone replacement therapy and radiological measures of sarcopenia.

Radiological Assessment					
First Author	Year	N	Age (years) – mean (sd)	Result	Length of follow-up & notes
Longitudinal Cohort					
Boyanov, M [46]	2005	44	51.8 (2.3)	No difference	1 year
Brown, M [43]	1997	44	65.5 (4.0)	No difference related to HRT	11 months With exercise
Figueroa, A [45]	2003	94	56 (2.3)	No difference related to HRT	1 year With exercise
Maddalozzo, G [44]	2004	167	51 (3.0)	No difference	1 year
Cross sectional					
Aubertin-Leheudre, M [51]	2005	40	59 (2.8)	No difference	
Bemben, D [50]	2002	40	59 (5.6)	No difference	
Costa, G [52]	2011	50	53 (4.7)	ASM greater with HRT (18.27 kg vs 16.14 kg)	
Gower, B [56]	2000	70	50 (3.0)	No difference	
Kim, SW [53]	2020	4254	64 (2.2)	Use of HRT for longer than 13 months reduced odds of sarcopenia (OR 0.60, 95% CI 0.41–0.88, $p = 0.01$).	
Mayo, C [56]	1998	882	62 (8.1)	No difference	
Muñoz, J [48]	2003	80	51 (2.5)	No difference	
Muñoz, J [49]	2002	57	50 (2.5)	No difference	
Onambele-Pearson, G [57]	2021	61	67 (6.8)	No difference	
Papadakis, G [67]	2018	1086	65 (6.8)	No difference	
Ronkainen, P [55]	2009	30	57 (1.8)	CT - higher relative thigh muscle area in HRT users (8 %, $p = 0.047$)	
Taaffe, D [47]	2005	840	74 (2.8)	CT - quadriceps muscle area greater (40.4cm^2 vs 39.1cm^2, $p = 0.001$), but not hamstring	
Walsh, M [58]	2006	82	57 (11)	No difference	

ALM – Appendicular Lean Mass, ASM – Appendicular Skeletal Muscle Mass, HRT – menopausal hormone replacement therapy 95%CI – 95 % confidence interval.

performance measures above this age only, but not for grip strength [61]. Only one article on grip strength had an average age > 65 years, showing grip strength was higher with HRT [47]. Three articles on physical performance had an average age > 65 years [41,47,60], with none showing a benefit from HRT. Four articles assessing muscle mass radiologically have an average age > 65 [43,53,57], with two suggesting possible benefit from HRT [47,53].

3.5.2. Women under age 60 at start of HRT use

RCT data: Two studies assessed grip strength with an average age under 60, both showing some improvement [25,32]. Two also assessed physical performance before 60 [25,30], but only one showed an improvement, in running speed and vertical jump height [30].

Six radiological studies looked at radiological measures before age 60. One using MRI did show and increase in cross-sectional muscle area, but only in one area [25]. One using CT showed an increase in two different areas assessed [30]. Three used DXA and showed a positive effect [25,27,28], but one only showed less deterioration in HRT users [26], and one showed no difference [29].

Observational Studies: No observational studies specifically report the age when HRT was initiated. However, all report the age at assessment, which would indicate HRT use started before this time.

Seven of 11 studies looked at grip strength with an average age under 60, but only 2 showed a positive effect of HRT [38,52], 5 did not [14,37,40,50,62]. Three physical performance studies were also younger [55,59,62], but only one showed a higher maximal walking speed [55].

Using radiological methods, 11 of 18 studies were under 60 [44–46,48–52,55,56,58], but only two showed HRT to have a positive relationship to muscle mass, one using DXA and one using CT [52,55].

3.5.3. Comparison between tibolone and oestrogen ± progestogen

RCT data: Only one study directly compared tibolone to oestrogen +/- progestogens [26]. This found that women taking tibolone or transdermal oestrogen maintained muscle mass, as assessed by DXA, whilst those taking oral micronized oestrogen or placebo declined.

Four studies compared tibolone to placebo only: Three assessed grip strength, with one administering 2.5 mg tibolone daily and showing benefit [32], and two administering tibolone 1.25 mg ("low-dose"), demonstrating no benefit [31,35]. Only one article assessed tibolone 1.25 mg and physical performance, demonstrating no benefit [31]. However, two assessing muscle mass radiologically did show a benefit, compared to placebo, one administering 1.25 mg tibolone [35], and the second administering 2.5 mg tibolone [27].

For comparison, in three articles administering oestrogen, one, using transdermal oestradiol, suggested improvement in grip strength [25]. For physical performance, five articles used oestrogen, with one showing improved running speed and vertical jump height [47]. For Radiological Assessment, eight articles used combinations containing oestrogen-based HRT, with four suggest benefit [25,26,28,30].

Observational data: No studies reported the effect of tibolone specifically on any outcomes assessed.

Our original protocol had also specified subgroup analyses for subtypes of consensus definition; use of testosterone; and initiation of HRT explicitly for peri-menopausal symptoms. No articles were able to contribute to these analyses.

4. Discussion

4.1. Interpretation of results

We identified 43 articles that examined the effect of peri-menopausal hormone replacement therapy on sarcopenia, 15 RCTs and 28 observational/non-randomised studies. There was no evidence examining the relationship between HRT use and consensus definitions of sarcopenia. Our ability to draw conclusions on related variables, including grip strength, physical performance and muscle quantity was very limited, as results were heterogenous, with methodologically weak, and at high risk of bias.

Looking at subgroups in more detail, the heterogeneity of outcomes to assess sarcopenia, along with the wide spectrum of HRT used, including timing, duration and differing formulations, are likely key reasons for lack of consistency in results.

4.1.1. Outcomes assessed

No study assessed sarcopenia using the most modern robust method, a consensus definition. However, as most of the definitions have only been developed in the past 10 years, and much HRT research was published before this, it is perhaps not surprising. Whilst this area could be fruitful for future research, but we are not aware of any pre-registered studies, either RCT or observational, which intend to assess this.

The effect of HRT on other outcomes available, grip strength, physical performance, and radiological assessment, generally showed similar results to one another, both in trial and observational data. The evidence of benefit was weakest for physical performance, and strongest for radiological assessment of muscle mass. However, for older adults and clinicians, measures of physical performance are probably the most important outcomes. Particularly considering the high/severe risk of bias of most studies, their results have limited meaning for clinicians and patients.

4.1.2. Timing of HRT

The idea of a 'window of opportunity' has been suggested for the effect of HRT on other conditions, such as cardiovascular disease, where there may be benefit in women under 60 years or within 10 years of menopause [63,64]. Trial data suggests that intervention in younger women, under 60 years, may have a greater effect than intervention in older women upon grip strength and radiological measures, but this was not clear for physical performance. One observational study stratified participants starting HRT within 5 years of menopause or after, and found benefit on physical performance confined to those starting within 5 years [61].

4.1.3. Duration of HRT

No studies with follow-up of 3 or more years showed any difference in measures of sarcopenia with HRT. However, most trials were much shorter, with a median duration of 1 year, and most observational studies were cross-sectional. This suggests that the positive results seen from shorter studies might only be a short-term effect, or potentially represent a publication bias. These shorter studies also showed more concerns for risk of bias, further limiting their impact.

4.1.4. Formulation of HRT

The effect of HRT on sarcopenia may vary according to drugs used, method of delivery (oral vs transdermal), and sequential vs. continuous combined approaches. Any observations here are compromised by the recorded data: many observational studies do not record the type of HRT used, and most RCTs did not separate their analysis by progestogen use.

Five trials assessed tibolone specifically, which is known to have greater androgenic properties. Whilst they consistently showed radiological benefits on muscle mass, only one showed benefit on grip strength, and none showed benefit in physical performance. However, doses used were inconsistent, and only one trial offered direct comparison to oestrogen-based HRT, with a high risk of bias.

Synthetic progestogens also have differing androgenic properties [65] Most trials here used MPA, which is considered reasonably androgenic compared to more contemporary progestogens (e.g., micronized progesterone, or less androgenic progestogens such as dydrogesterone). Therefore, the available data may be of less relevance to women and clinicians today.

Three RCTs used transdermal oestrogen patches, with two of three showing benefit on radiological assessment of muscle mass, compared to two of seven studies using oral oestrogen. However, there was heterogeneity of progestogen usage, making direct comparison difficult. Only one study using transdermal oestrogen assessed grip strength and physical performance, making comparisons problematic.

Clinical practice also differentiates between continuous-combined HRT and sequential HRT, which was not consistently reported in the literature; we have not been able to draw any conclusions on this point.

4.2. Strengths

Our search strategy was systematic and wide, encompassing major databases of interest and grey literature. Our analysis benefitted from including both trial and observational data. Whilst some outcomes have shown divergent results between trial and observational studies on HRT, we are able to demonstrate that study design is not the primary cause of heterogeneity in our findings.

4.3. Limitations

We were unable to identify studies using a modern, "gold standard" outcome: a consensus definition of sarcopenia. Our findings were also unsuitable for meta-analysis. The underlying populations of women in both the observational and trial articles were quite different with high heterogeneity ($I^2 > 90$ %), due to different population ages, locations, and formulations of HRT used. Combined with different methods of reporting most results, this unfortunately precluded meaningful meta-analysis.

Furthermore, meta-analysis would also likely have been dominated by the much greater population size in articles using data from the WHI trial. This is now interpreted with much caution, as many women included were significantly post-menopausal at enrolment, when initiating HRT is no longer routinely recommended, and with an older HRT formulation. The trial itself was terminated early, with a high rate of unblinding, and high dropout rates [66]. Furthermore, 20/43 studies included have fewer than 100 participants, and may have been underpowered to detect an effect.

Only 2 studies, both observational, were outside of Europe/North America, limiting world-wide generalisability of most data. Many articles we identified were published over two decades ago. As a result, the regimens used, such as CEE with MPA, are no longer routinely prescribed to women starting HRT, limiting the applicability of our studies to current practice. Furthermore, it would no longer be common to initiate HRT in women who are many years post-menopausal, as was done in some RCTs, and may have occurred in observational studies.

In assessing publication bias, we were unable to construct formal funnel plots, due to high heterogeneity of study populations, different measurements of sarcopenia-related parameters reported, and limited reporting of required measures of error. Whilst some key studies on women's health are included, such as the WHI trial, we cannot exclude a bias against smaller negative trials and negative observational studies. We have tried to mitigate against this by searching grey literature, and including conference abstracts, where negative results might be more readily presented, whilst remembering that these sources are often methodologically weaker.

Although we were able to look at formulations of HRT in RCTs in a limited fashion, this was not possible for observational studies, as they did not routinely report formulations of HRT used by women. Observational studies were all at high or critical risk of bias. Over half did not include adjustment for confounding at all in comparing measurements of sarcopenia, using methods such as ANOVA (Appendix D – Supplementary Table D1). Many studies did not even report important confounders, such as physical activity or socio-demographic variables. A number implemented restrictive inclusion/exclusion criteria instead, such as specifying limited levels of physical activity, or no "major" medical comorbidities. There was also limited reporting and no analysis of female-specific parameters related to reproductive health, such as parity, or surgical vs spontaneous menopause, although these may also be related to sarcopenia. There was also no discussion of indications for

HRT in observational studies. The reported results therefore offer limited information.

5. Conclusion

We have identified 43 articles assessing the effect of HRT on sarcopenia and sarcopenia-related measures. There was no published data on sarcopenia prevention defined by currently accepted consensus definitions, our primary outcome, and overall data quality was poor, with a high risk of bias. Inconsistent evidence of benefit was found for sarcopenia-related measures. Trial data suggests a positive impact on radiological assessment of muscle mass, but no consistent evidence that HRT was associated with improved handgrip strength or physical performance. Studies also used older regimens of HRT, and examination of the effects of modern regimes of HRT has not been conducted. Whether timing of initiation and cessation of HRT might impact any long-term effects is not clear.

As HRT is increasingly used, and appears safer and affordable than previously, future studies are needed using the accepted consensus group definitions of sarcopenia, including more recent HRT regimens, with sufficient follow-up and participants.

Contributors

Marc F Österdahl conceived the study and conducted the searches, extracted data, conducted quality assessments, and wrote the first draft of the manuscript. Mary Ni Lochlainn reviewed studies for inclusion and reviewed the manuscript. Carly Welch was involved with the development of the study and reviewed the manuscript. Janice Rymer was involved with the development of the study and reviewed the manuscript. Mark Ashworth was involved with the development of the study and reviewed the manuscript. Julie Whitney advised on conduct of the systematic review and search strategy, and reviewed the manuscript. Emma L Duncan conceived the study and reviewed and revised the manuscript. Claire J Steves conceived the study and reviewed and revised the manuscript. All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Ethical approval

This paper is a systematic review, requiring no new contact with research participants nor members of the public, and is therefore not subject to ethical review.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

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Declaration of competing interest

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Appendix A. Supplementary data

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