

## REVIEW - SYSTEMATIC

# Effect of hormone therapy on muscle strength in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials

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### Abstract

**Objective:** This study aimed to evaluate the overall effects of hormone therapy (HT) on muscle strength in postmenopausal women through a systematic review and meta-analysis.

**Methods:** PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched from the inception dates to August 2019. Randomized controlled trials (RCTs) that compared the effects of HT with either no therapy or placebo on muscle strength in postmenopausal women were eligible. The quality of studies was assessed using the Cochrane risk of bias tool. Measurements of changes in muscle strength compared to baseline were extracted for pooled analysis. The effect size was calculated as standardized mean differences using a random effects model.

**Results:** We identified nine studies with a combined population of 2,476 postmenopausal women. The studies included were assessed to be of good quality overall. The results showed that HT was not associated with muscle strength gain in postmenopausal women (standardized mean difference = 0.352; 95% confidence interval, -0.098 to 0.803;  $P = 0.125$ ;  $I^2 = 95.3\%$ ). The changes in muscle strength in women receiving HT were not significant. The results were unchanged when stratified by treatment type, muscle group, and treatment duration.

**Conclusions:** The use of HT was not associated with the improvement of muscle strength in postmenopausal women. This finding suggested that HT might not improve muscle strength or that the effect size was too small to identify significant therapeutic efficacy.

**Key Words:** Hormone therapy – Muscle strength – Postmenopausal woman – Systematic review.

Sarcopenia is a common disease in older people characterized by progressive and generalized loss of muscle mass and muscle strength, especially in elderly women.<sup>1</sup> The prevalence of sarcopenia is estimated to be 5% to 13% in individuals between 60 and 70 years of age.<sup>2</sup> It increases to 6% to 59% in women older than 60 years.<sup>2-4</sup> In Asia, the estimated prevalence is around 8% to 12% in the postmenopausal women.<sup>5,6</sup> Deterioration of muscle quality and quantity affects many aspects of body function, including

an increased risk of fall and fracture, impaired cardiopulmonary function, mobility restriction, functional limitation, and physical disability.<sup>7-9</sup> These lead to poor quality of life,<sup>1</sup> loss of independence or need for long-term care placement, and death<sup>1,10</sup> in older adults. Recent studies have also shown that sarcopenia is associated with metabolic disturbances such as atherosclerosis, type 2 diabetes, and hypertension.<sup>11</sup> European consensus on sarcopenia proposed muscle strength as a primary measure in the assessment of sarcopenia,<sup>12</sup> based on its potential to be a strong predictor of functional capacity, risk of hospitalization, and mortality.<sup>13,14</sup> Effectively decreasing the loss of muscle strength may be closely related to the decrease in functional impairment and economic burden on aging people.

Hormone changes can be another important influence on the development of sarcopenia in elderly women. Menopause is a special transition for women and is characterized by a rapid decline of ovarian hormones.<sup>15</sup> It was suggested to be an independent predictor of decreased muscle strength and balance.<sup>16-18</sup> Samson et al<sup>18</sup> observed a steep decline in muscle strength among women older than 55 years. Another cohort study suggested that menopause was associated with decreasing muscle strength.<sup>17</sup> In addition, Cheng et al<sup>16</sup> reported that postmenopausal women had an average of 4.2 kg less grip

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strength than premenopausal women after controlling for confounding factors such as age and body mass index. Hormone therapy (HT) is generally used to counter the changes caused by the loss of ovarian hormones. The benefits in women who undergo HT include a reduced risk of all-cause mortality, menopausal symptoms, osteoporosis, and new-onset diabetes mellitus and an improvement in quality of life.<sup>19</sup> The commonly used types of HT includes estrogen alone, estrogen plus progestogen, synthetic steroids (eg, tibolone), and selective estrogen receptor modulators (eg, raloxifene).<sup>20</sup>

Evidence on the effect of HT on muscle strength remains inconsistent. Some studies have found that HT could improve muscle strength,<sup>21,22</sup> whereas other studies argue that HT has no effect on improving muscle strength.<sup>23,24</sup> In 2009, a meta-analysis including both observational and experimental studies reported that HT improved muscle strength.<sup>25</sup> Most of the studies included in that meta-analysis were cross-sectional studies (~65%), which have the intrinsic limitation of being unable to establish the causality between exposure and outcome. In addition, more randomized controlled trials (RCTs) were conducted and published after the year 2009. Among them, a large RCT study in 2010 found no significant improvement in muscle strength after HT.<sup>26</sup> Controversy still exists regarding the effect of HT on muscle strength of postmenopausal women. Various intervention types using HT and treatment durations adopted in different studies could be adding to this confusion.

HT has been used in routine clinical practice for more than 70 years, especially in postmenopausal women.<sup>27,28</sup> The findings about its effect on muscle strength thus far are promising but inconclusive. Summarizing evidence obtained from RCTs of HT and muscle strength in postmenopausal women could be of great interest. Therefore, in this systematic review and meta-analysis, we incorporated recent and previously published RCTs and evaluated the impact of HT on muscle strength in postmenopausal women.

## METHODS

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines<sup>29</sup> (see Table, Supplemental Digital Content 1, <http://links.lww.com/MENO/A579>, for the checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The protocol for this study was available in the PROSPERO registry (CRD42019147779).

### Literature search and study selection

Electronic databases searched included PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials until August 2019. The following keywords and search parameters were used: (1) hormone therapy or estrogen, (2) skeletal muscle OR muscle mass OR muscle strength OR lean mass OR fat-free mass OR sarcopenia OR muscle function OR physical performance, (3) (woman OR

female) AND human, (4) (1) AND (2) AND (3). As a strategy to reduce bias, we also scanned the references of narratives and systematic reviews to identify any potential studies that were not retrieved through our search (see document, Supplemental Digital Content 2, <http://links.lww.com/MENO/A580>, for the details of search strategy in each database).

RCTs that met the following criteria were included: the participants were postmenopausal women; the study included both HT and control (no treatment or placebo) groups; the study reported a clear intervention duration; the pretest and posttest measurements of muscle strength (ie, handgrip strength and maximal voluntary contractions with any muscle group/action) were available. We excluded studies if the participants had any condition or disorder that might influence muscle strength (eg, evidence of hereditary or acquired muscular disease); if the intervention of the treatment group was not HT alone, but combined with another intervention such as exercise; and if the language was not English.

Titles and abstracts were screened by two independent reviewers (Y.X., Y.-Q.M.) to determine whether studies met the inclusion criteria. The full text article was then reviewed when both reviewers agreed that a study was eligible. A third reviewer (T.-F.X.) was available to arbitrate when there were inconsistencies.

### Data extraction and study quality assessment

Two independent reviewers (Y.X., K.-L.D.) extracted the data using a predesigned electronic data extraction form (Table S5, see document, Supplemental Digital Content 3, <http://links.lww.com/MENO/A581>). The form was piloted using two of the included studies. It was evaluated by the two reviewers and was further discussed whether there were any required changes. If there was an inconsistency, a third reviewer (T.-F.X.) would check the data and make a decision. For each selected study, data collected included (a) basic study information, including author name, study year, country of origin, and inclusion and exclusion criteria; (b) characteristics of the study population, including age, menopause age, sample size, duration of follow-up; (c) details of HT type and administration (eg, oral, transdermal, vaginal) and the medication dose and duration; and (d) the pre- and post-intervention measurements of muscle strength in each group with mean and standard deviation (SD). The change in muscle strength was used to calculate the effect size. For some data that were required for the meta-analysis that were missing, we would contact the authors of these studies for additional information.

The study quality was assessed using the Cochrane Collaboration risk-of-bias tool, with assessments of low risk, high risk, or unclear risk.<sup>30</sup> Included studies were independently assessed by two reviewers (Y.X., K.-L.D.), with details including method of random sequence generation, allocation concealment, blinding implementation, selection bias, and other sources of bias. If the disagreement between the two reviewers was not resolved by discussion, then a third reviewer (T.-F.X.) was available to arbitrate.

### Primary outcome and data synthesis

The change in muscle strength was the primary outcome in this study. We extracted the mean difference and SD of the change in muscle strength (final measurement minus baseline measurement) from each study. For studies that did not report the mean difference, the mean and SD of baseline and end line measurements were used to calculate the change in muscle strength using the following equation:

$$\left[ \left( SD_{\text{pre}}^2 + SD_{\text{post}}^2 \right) - \left( 2r \times SD_{\text{pre}} \times SD_{\text{post}} \right) \right]^{\frac{1}{2}}$$
<sup>30,31</sup> In this equation,  $r$  is the correlation coefficient between pretest and posttest values in the same group; however, none of the included studies reported the correlation coefficient. To solve this problem, we applied a method reported in the Cochrane handbook to compute for the correlation

coefficient: 
$$\frac{\left( SD_{\text{baseline}}^2 + SD_{\text{final}}^2 - SD_{\text{change}}^2 \right)}{\left( 2 \times SD_{\text{baseline}} \times SD_{\text{final}} \right)}$$
<sup>30</sup> The Hedges-Olkin method was used to calculate the overall correlation coefficient.<sup>31</sup> The final estimated correlation coefficient of the experimental and control groups for muscle strength was 0.87.

If the data for a study were presented as mean and standard error, the SD could be calculated using the study sample size. When a study measured muscle strength in more than one muscle group (eg, forearm flexors, knee extensors), the effect sizes and their variances were averaged across the muscle groups.<sup>31</sup> If studies included multiple time points, data from the last time point were used in the overall meta-analysis. When a study contained more than one treatment arm (eg, two intervention groups compared with two different control groups), each treatment arm was included in the meta-analysis independently. If different categories of estrogen were used in experimental groups and compared to a single control group, the shared control group was evenly split into more groups with smaller sample sizes in accordance with the number of experimental groups.<sup>30</sup>

### Statistical analysis

For eligible studies, random effects model meta-analyses were performed to determine the effect of HT on muscle strength. We used the standardized mean difference (SMD) and its 95% confidence interval (95% CI) to present the effect sizes of HT on muscle strength. SMDs of 0.2 or lesser, 0.5, and 0.8 were considered to represent small, medium, and large effects, respectively.<sup>32</sup> Heterogeneity among the studies' effect sizes was assessed by  $\chi^2$  test and the inconsistency was quantified by the  $I^2$  statistic. Subgroup analyses were conducted to detect the potential influences of factors on the summary effect size, including treatment duration (ie,  $\leq 1$  year and  $> 1$  year), HT types (ie, estrogen plus progestogen and tibolone), and various muscle groups (ie, forearm flexors and knee extensors). Meta-regression was also performed for HT types, muscle groups, and treatment duration, respectively. Sensitivity analysis was used to detect the impact of a specific study on the summary effect size. We performed the sensitivity analysis by repeating the meta-analysis after removing the study assessed to have high risk of bias based on the results

of study quality assessment. The difference between two estimated effect size was evaluated.<sup>33</sup> Egger's test, Begg's test, and a funnel plot were used to test for publication bias. Duval and Tweedie's trim and fill test was also used to make a correction for the effect of possible bias. STATA 15.0 software was used to analyze the data. A  $P$  value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### Description of included studies

#### Results of the search

Overall, we identified 15,465 articles from three databases. Of these, 1,464 were excluded due to duplication, leaving 14,001 articles for screening. After the first screening based on the abstracts and titles, we excluded 13,964 articles. The full texts of the remaining 37 potentially relevant studies were assessed according to the predefined inclusion and exclusion criteria. Finally, nine studies were included for analysis in this study. The study selection process and reasons for exclusion are presented in Figure 1. The detailed information about the exclusion of irrelevant studies is shown in Tables S2 to S4 (see document, Supplemental Digital Content 3, <http://link.s.lww.com/MENO/A581>).

#### Included studies and design

In total, nine RCTs examining the effect of HT on muscle strength were included. The basic characteristics of the nine selected studies are shown in Table 1.

#### Duration of trials

The duration of these nine studies ranged from 6 months to 6 years. There were six studies with the treatment duration less than 1 year,<sup>22,24,34-37</sup> two studies with 2 years,<sup>38,39</sup> and one study with 6 years.<sup>26</sup>

#### Participants and setting

A total of 2,476 participants (HT group: 1,290; control group: 1,186) were included in the analysis. The participants in the nine studies were postmenopausal women from 45 to 79 years of age.<sup>22,24,26,34-39</sup> Seven of these nine RCTs excluded individuals who had taken estrogenic medication within 6 months before the study began.<sup>22,34-39</sup> Among these nine studies, two studies were conducted in England,<sup>22,24</sup> two in Finland,<sup>34,38</sup> two in Sweden,<sup>35,36</sup> two in Netherlands,<sup>37,39</sup> and one in the USA.<sup>26</sup>

#### Types of intervention and outcomes

The types of HT were estrogen plus progestogen, estrogen alone, tibolone, and raloxifene. Among the nine studies, three studies had two treatment arms.<sup>26,38,39</sup> Six of the 12 treatment arms were estrogen plus progestogen,<sup>22,26,34,35,38</sup> three were tibolone,<sup>36,37,39</sup> one was raloxifene,<sup>39</sup> one was estrogen alone,<sup>26</sup> and one was mixed types.<sup>24</sup> The mode of administration for HT in four studies was oral and was unclear for the other five studies.

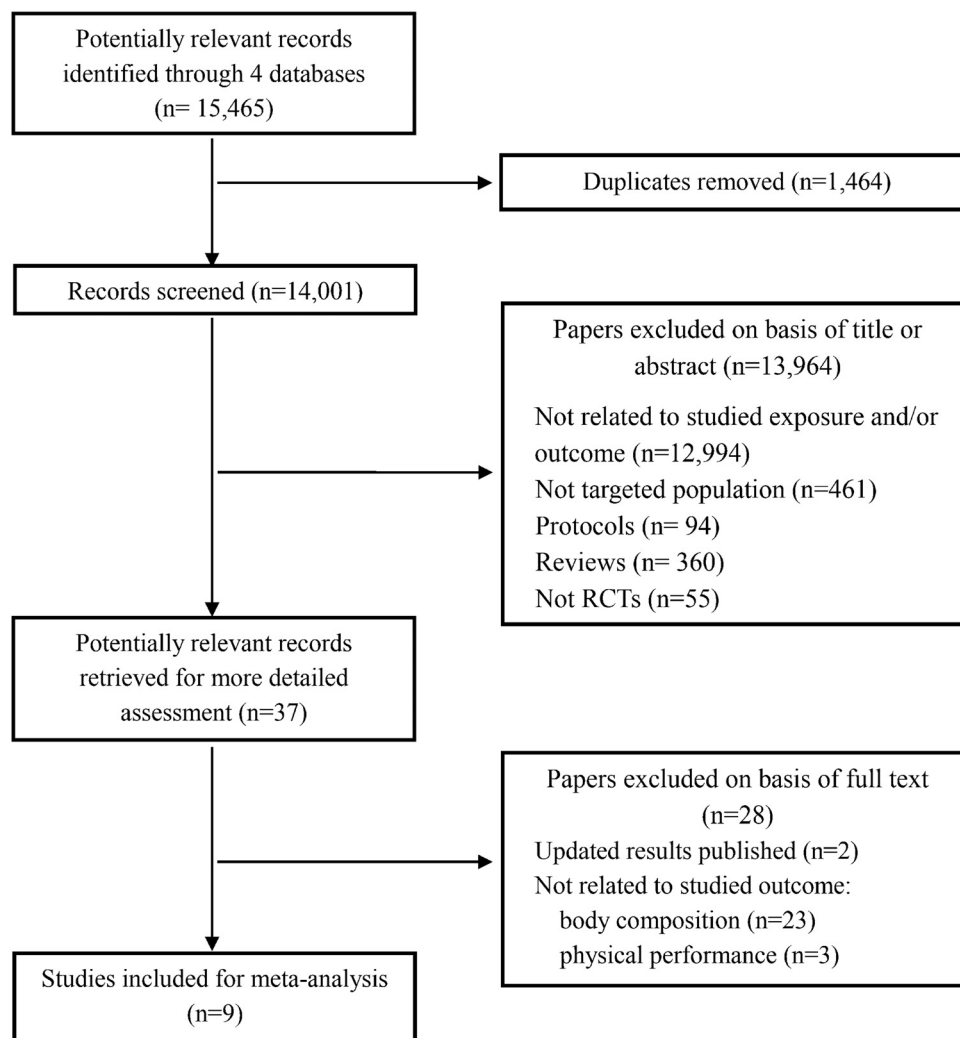


FIG. 1. The screening flow chart of study selection process.

TABLE 1. Characteristics of the included studies and participants

Author, year	Country	Age, y	YSM, y	Number (HT/no HT)	HT types (doses)	Mode of administration	Outcomes	Duration
Skelton et al, <sup>22</sup> 1999	England	61	5.0-15.0	37/48	CO (0.625 mg) and norgestrel (0.15 mg)	NA	Adductor pollicis strength	12 mo
Heikkinen et al, <sup>38</sup> 1997	Finland	49-55	0.5-3.0	51/25	EV (2 mg) and MPA (10 mg or 20 mg) <sup>a</sup>	NA	Back extensor strength	24 mo
Armstrong et al, <sup>24</sup> 1996	England	45-70	NA	54/54	Prempak C or Premarin 0.625 mg	NA	Leg extensor power, handgrip strength	12 mo
Taaffe et al, <sup>34</sup> 2005	Finland	50-57	0.5-5.0	14/15	E <sub>2</sub> (2 mg) and norethisterone acetate (1 mg)	Oral	Knee extensor strength	12 mo
Ribom et al, <sup>35</sup> 2002	Sweden	60-78	NA	17/17	E <sub>2</sub> (4.3 mg) and MP (2.5 mg)	NA	Knee extensor and flexor strength, handgrip strength	6 mo
Michael et al, <sup>26</sup> 2010	America	65-79	NA	851/853	CEE (0.625 mg) and MPA (2.5 mg), CEE (0.625 mg) <sup>a</sup>	NA	Handgrip strength	6 y
Ribom et al, <sup>36</sup> 2011	Sweden	60	17.6	34/35	Tibolone (1.25 mg)	Oral	Knee extensor strength, handgrip strength	6 mo
Meeuwssen et al, <sup>37</sup> 2002	The Netherlands	54	≥1.0	39/42	Tibolone (2.5 mg)	Oral	Knee extensor strength	12 mo
Jacobsen et al, <sup>39</sup> 2012	The Netherlands	74	NA	193/97	Tibolone (1.25 mg), raloxifene (60 mg) <sup>a</sup>	Oral	Handgrip strength	24 mo

CEE, continuous conjugated estrogens; CO, conjugated estrogens; CPA, cyproterone acetate; E<sub>2</sub>, 17β estradiol; EV, estradiol valerate; HT, hormone therapy; mo, month; MP, medroxyprogesterone; MPA, medroxyprogesterone acetate; NA, not available; y, year; YSM, years since menopause.

<sup>a</sup>Studies have more than one intervention groups with different types of HT.

TABLE 2. Quality assessment of the nine included studies with low, high, or unclear risk of bias

Author, year	Random sequence generation	Allocation concealment	Binding of participants and personnel	Binding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Armstrong et al, <sup>24</sup> 1996	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
Heikkinen et al, <sup>38</sup> 1997	Unclear	Unclear	High	Low	Low	Unclear	Unclear
Skelton et al, <sup>22</sup> 1999	Unclear	Unclear	High	Low	High	Unclear	High
Ribom et al, <sup>35</sup> 2002	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Meeuwsen et al, <sup>37</sup> 2002	Low	Low	Low	Low	Low	Unclear	Unclear
Taaffe et al, <sup>34</sup> 2005	Low	Low	Low	Low	Low	Unclear	Unclear
Michael et al, <sup>26</sup> 2010	Low	Low	Unclear	Low	Low	Low	Unclear
Ribom et al, <sup>36</sup> 2011	Low	Low	Low	Unclear	Low	Unclear	Unclear
Jacobsen et al, <sup>39</sup> 2012	Low	Low	Low	Unclear	Low	Unclear	Unclear

Three of nine studies measured the muscle strength of more than one muscle group.<sup>24,35,36</sup> Among these, five examined forearm flexors,<sup>24,26,35,36,39</sup> four examined knee extensors,<sup>34-37</sup> one examined knee flexors,<sup>35</sup> one examined thumb adductors,<sup>22</sup> one examined back extensors,<sup>38</sup> and one examined leg extensors.<sup>24</sup>

### Quality assessment of studies

Nine studies were evaluated for a total of 63 assessment items. The results showed that the overall quality was good, with only 4 of 63 items assessed to be at high risk; only one trial had a high risk of bias in three of six domains.<sup>22</sup> Seven studies reported an adequate and clear random sequence generation procedure.<sup>24,26,34-37,39</sup> Four studies attempted to blind the participants and observers to decrease the risk of bias.<sup>34,36,37,39</sup> Six studies reported clear blinding of outcome assessment.<sup>22,24,26,34,37,38</sup> Eight studies that provided the details and methods used to handle the missing data of

participants who were lost to follow-up.<sup>24,26,34-39</sup> The details of the overall quality assessment are summarized in Table 2.

### Main analysis

As illustrated in Figure 2, the result from the random effects meta-analysis indicated that HT had no significant effect on the improvement of muscle strength in postmenopausal women (SMD = 0.352; 95% CI, -0.098 to 0.803;  $P = 0.125$ ;  $I^2 = 95.3\%$ ;  $n = 12$ ). No significant difference was seen in changes in muscle strength between women who took HT and those who did not.

### Subgroup analysis and metaregression

The subgroup analyses were performed according to HT types, treatment duration, and measurement of muscle strength in different muscle groups. The subgroup analysis of HT type was only conducted for the estrogen plus progestogen group ( $n = 6$ ) and the tibolone group ( $n = 3$ ). For the

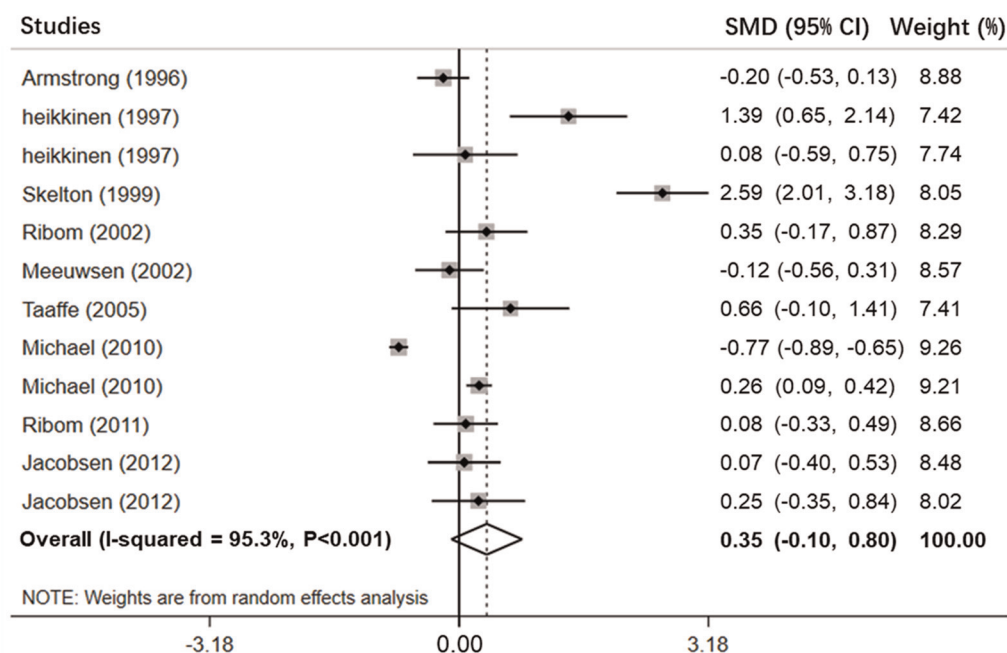
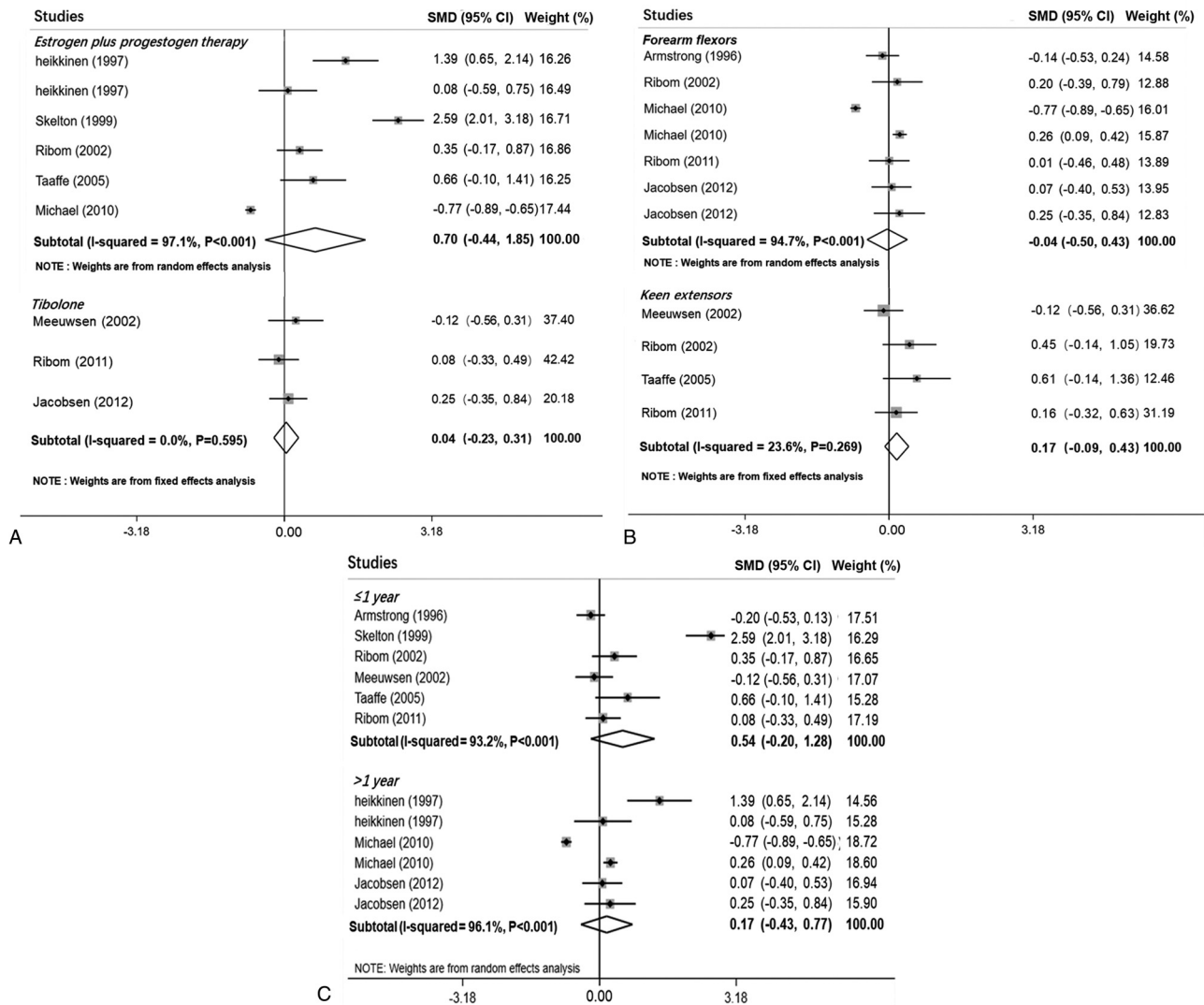


FIG. 2. Forest plot of effect size from nine studies that assessed muscle strength in postmenopausal women who were and were not using HT. For each study, central diamond indicates effects, line means the 95% CI of effects, and grey square reflects the study's weight in the pooling. The hollow diamond represents the overall estimated effect and its 95% CI. CI, confidence interval; SMD, standardized mean difference.



**FIG. 3.** Forest plot of the subgroup analysis with different (A) HT types, (B) muscle groups, and (C) treatment duration. For each study, central diamond indicates effects, line means the 95% CI of effects, and grey square reflects the study's weight in the pooling. The hollow diamond represents the subtotal estimated effect and its 95% CI. CI, confidence interval; SMD, standardized mean difference.

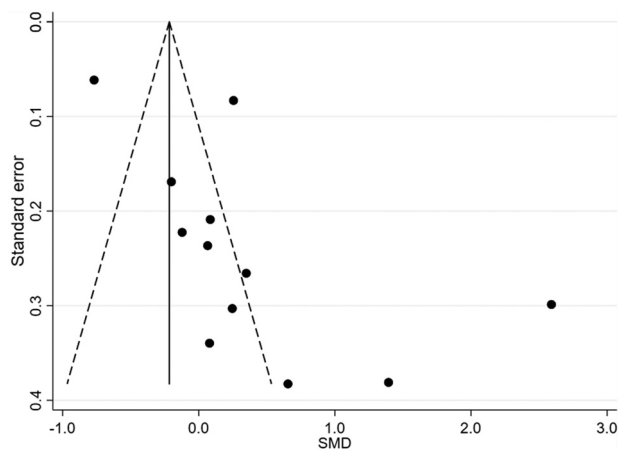
estrogen plus progestogen group, five studies including six treatment arms with 1,364 participants were analyzed. The results showed that treatment using combined hormones was not associated with muscle strength gain (SMD = 0.704; 95% CI, -0.438 to 1.845;  $P = 0.227$ ;  $I^2 = 97.1%$ ;  $n = 6$ ; Fig. 3A) in postmenopausal women. Three studies including 221 individuals were used to detect the treatment effect of tibolone on muscle strength, and no significant association was identified (SMD = 0.04; 95% CI, -0.227 to 0.307;  $P = 0.769$ ;  $I^2 = 0.0%$ ;  $n = 3$ ; Fig. 3A). No significant difference was observed between the estrogen plus progestogen group and the tibolone group ( $P = 0.267$ ).

Three of the included studies measured the muscle strength of more than one muscle group (ie, forearm flexors and knee extensors). Five studies including seven treatment arms and four studies reported data about muscle strength at the forearm flexors and knee extensors, respectively. For the subgroup

analysis of forearm flexors, the SMD was -0.036 (95% CI, -0.503 to 0.432;  $I^2 = 94.7%$ ;  $P = 0.881$ ;  $n = 7$ ; Fig. 3B); and for knee extensors, the SMD was 0.170 (95% CI, -0.094 to 0.434;  $I^2 = 23.6%$ ;  $P = 0.221$ ;  $n = 4$ ; Fig. 3B). There was no significant difference between the subgroups ( $P = 0.475$ ).

Considering the potential varied influences of different treatment durations on muscle strength, we divided treatment duration into two subgroups ( $\leq 1$  and  $> 1$  year). For the group with 1 year or less, the SMD was 0.539 (95% CI, -0.199 to 1.276;  $I^2 = 93.2%$ ;  $P = 0.152$ ;  $n = 6$ ; Fig. 3C), and for the group with more than 1 year, the SMD was 0.169 (95% CI, -0.428 to 0.766;  $I^2 = 96.1%$ ;  $P = 0.579$ ;  $n = 6$ ; Fig. 3C). The difference between the two subgroups was not significant ( $P = 0.445$ ).

Subgroup analysis was not performed for the other HT types and for muscle strength of other muscle groups due to the limited study number ( $n < 2$ ). The meta-regression also



**FIG. 4.** Funnel plot for publication bias of 9 studies with 12 treatment arms.

found no significant factors that might influence the effect of HT on muscle strength ( $P > 0.05$ ).

### Sensitivity analysis and publication bias

After excluding the single trial with a high risk of bias<sup>22</sup> (ie, limiting the meta-analysis to studies with low or moderate risk of bias), the repeating meta-analysis showed no notable change in the summary effect size (SMD = 0.142; 95% CI, -0.240 to 0.524;  $I^2 = 93.1\%$ ;  $P = 0.465$ ). Figure 4 shows the funnel plot for the included studies. Although the funnel plot of standard error by effect size (SMD) was slightly asymmetric, the results of Egger's test ( $P = 0.058$ ) and Begg's test ( $P = 0.052$ ) indicated a low likelihood of publication bias. In addition, the Duval and Tweedie's trim and fill test was also used to make a correction for the result. After the correction with three possible missing studies, the result still showed that HT had no significant effect on the improvement of muscle strength in postmenopausal women (SMD = 0.621; 95% CI, -0.039 to 1.282;  $P = 0.065$ ). Based on the negative results, the possibility was low that the articles with positive results were published, whereas the negative articles were unpublished. Thus, there was low probability that the publication bias might influence the results in this study.

## DISCUSSION

This systematic review and meta-analysis investigated the effects of HT on muscle strength in postmenopausal women based on data from nine RCTs. The results showed that HT was not associated with improvement of muscle strength in postmenopausal women. The subgroup analyses of various muscle groups, HT types, and treatment duration also found no effect of HT on muscle strength.

Findings from this study supported that HT has no benefit for improving muscle strength in postmenopausal women. In recent years, the association of the sharp decline of estrogen levels in postmenopausal women with sarcopenia garnered much attention. Several studies evaluated whether HT could improve muscle quality and function.<sup>40-43</sup> A systematic

review and meta-analysis published in 2019 found no association between the intervention of HT and an increase in muscle mass.<sup>44</sup> This was important because muscle mass or fiber size was suggested to be a determinant of muscle strength.<sup>45</sup> The results regarding muscle mass supported the findings in this study and could imply that HT might not improve muscle strength via prevention of muscle mass loss. In addition, studies found that type II fibers (fast fibers) could have higher capacity for force generation than type I muscle fibers (slow fibers).<sup>46</sup> The cross-sectional area of muscle fiber decreases and its composition of fiber types shifts to a slower profile with aging.<sup>47</sup> A shift of distribution to faster fibers might increase the overall specific force of the muscle; however, one study found no difference in the distribution of slow and fast muscle fibers between individuals who underwent HT and those who did not.<sup>41</sup> The distribution of fiber types was also observed to be independent of HT status.<sup>41</sup>

The lack of a significant relationship between HT and muscle strength might also be partially explained by low quantities of estrogen receptors (ER) for HT to act on muscle in postmenopausal women. Estrogen exerts its biologic actions through ER. Two studies found that ER may be expressed more highly in type I fibers than in type II fibers.<sup>48,49</sup> Wiik et al<sup>49</sup> also revealed the positive correlation between the expression levels of ER and type I fiber percentage in humans. In addition, one study argued that aging or prolonged duration of estrogen deficiency might lead to a decline in muscle ER and that this might affect the metabolic action of HT in postmenopausal women.<sup>50</sup>

Another presumed reason for the lack of association between HT and improvement in muscle strength was that the impact of aging on muscle was strong and inevitable. Aging is the major factor that accelerates the deterioration of muscle wasting. The age-related decline of muscle function might be already too severe in the postmenopausal women and thus concealed any moderate positive effect of HT.<sup>39</sup> The potential benefits of HT for muscle strength might not be observed due to the advancing age of the study population.

A systematic review and meta-analysis on this topic was published in 2009. It reported that HT improved muscle strength,<sup>25</sup> while the findings from that meta-analysis were based on a combined analysis of observational and experimental studies with approximately 65% being cross-sectional studies. The biases and limitations inherent to the design of a cross-sectional study must be considered. To also reduce the heterogeneity derived from varied study designs, we performed this meta-analysis including only RCTs. RCTs could provide a higher quality of evidence for causality than the observational study design. Furthermore, four additional RCTs that were not included in the previous study were incorporated into the analysis in this study. All four studies reported a neutral association between HT and muscle strength. Overall, the quality of the trials included in this study was assessed to be good. A more exact estimation of the relationship between HT and muscle strength may be obtained

from this study. In addition, we focused on the potential effects of various HT types, which were not covered in previous analyses. The associations between various HT types and muscle strength were also not significant in the subgroup analysis, whereas the results showed that the heterogeneity for the tibolone subgroup was largely reduced. This might imply that the various types or doses of HT might affect potential efficacy on muscle strength. Data on dosage and mode of administration were insufficient, which made it difficult for us to explore these factors further.

HT might not be a very effective treatment for sarcopenia in postmenopausal women. HT has been prescribed for decades for the treatment of postmenopausal symptoms.<sup>51</sup> It may benefit the prevention and treatment of some disorders such as osteoporosis in postmenopausal women.<sup>19</sup> The harmful effect of increasing the risk of developing breast cancer and pulmonary embolism was also reported.<sup>19</sup> This meta-analysis of RCTs revealed that HT was not associated with improvement of muscle strength in postmenopausal women. The effectiveness of HT for improving or maintaining muscle strength might be weak in postmenopausal women.

Several limitations should be considered. A limitation of this study is the heterogeneity detected among included studies. The random effects model was used to minimize this effect as much as possible. Another limitation is the lack of information on differences in physical activity among different studies. Information on this factor is important because physical activity is strongly related to muscle strength. Finally, the subgroup analyses were based on the relatively small number of studies and participants, which limits study power.

## CONCLUSIONS

In this systematic review and meta-analysis of RCTs, the use of HT was not associated with improvement of muscle strength in postmenopausal women. This finding suggested that HT had no benefit for muscle strength improvement or that the effect size was too small to have a significant therapeutic efficacy.

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