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Meta-Analysis

Pharmacological interventions to improve bone density in functional hypothalamic amenorrhea: a systematic review and network meta-analysis of randomized clinical trials

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Abstract

Context **Women with functional hypothalamic amenorrhea (FHA) are at high risk of poor bone health. When lifestyle measures fail to restore menses, pharmacological interventions are needed for bone health, but comparative efficacy remains unclear.**

Objective **To compare the efficacy of available pharmacological interventions to improve bone mineral density (BMD), in women with FHA, employing network meta-analysis (NMA).**

Data sources **Medline, Embase, Emcare, Cochrane CENTRAL, ISRCTN, and ClinicalTrials.gov were searched up to 20 September 2025.**

Study selection **Eligible randomized-controlled trials evaluated pharmacological interventions for lumbar spine (LS), femoral neck (FN), or total hip (TH) BMD in women with FHA. Two independent reviewers screened titles, abstracts, and texts.**

Data Extraction **Two reviewers independently extracted data following the Preferred Reporting Items for Systematic Reviews-network meta-analysis guidelines. Outcomes were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs) using random-effects NMA. Evidence certainty was assessed with CINeMA.**

Data Synthesis & Results **Thirteen randomized-controlled trials (n = 897 participant observations across all pharmacotherapy comparisons) were included (LS BMD: $n = 897$; FN BMD: $n = 370$; TH BMD: $n = 750$). *Transdermal* hormone replacement therapy (HRT) was superior to control (placebo or no intervention) for LS BMD with SMD: 0.34 (0.03, 0.64) and FN BMD with SMD: 0.57 (0.04, 1.10). *Oral* HRT and the combined oral contraceptive pill (COCP) showed no significant benefit for any BMD site. Teriparatide was superior to *transdermal* HRT and COCP for LS BMD with SMDs: 1.48 (0.38, 2.59) and 1.75 (0.66, 2.83), but not FN or TH BMD.**

Conclusions ***Transdermal* HRT and teriparatide improve LS BMD in women with FHA, with *transdermal* HRT also improving FN BMD.**

Study registration **PROSPERO (CRD42024576872).**

Keywords osteoporosis, hypothalamic amenorrhea, anorexia nervosa, hormone replacement therapy, combined oral contraceptive pill

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Functional hypothalamic amenorrhea (FHA) is a common reproductive disorder characterized by chronic anovulation due to stress, weight loss, excessive exercise, alone or in combination (1). FHA causes 30% of secondary amenorrhea in women of reproductive age and affects 17.4 million women worldwide (2), making it one of the commonest reproductive disorders encountered in clinical practice (3). The management of FHA, including resultant low bone mineral density (BMD), involves a multidisciplinary healthcare team including endocrinologists, rheumatologists, general practitioners, orthopedic surgeons, gynecologists, dieticians, and psychologists (1).

FHA is a state of estrogen deficiency leading to detrimental skeletal effects, including insufficient peak bone mass accrual if onset is in adolescent/early adult life, low BMD, impaired bone microarchitecture, and resultant increased fracture risk (4). Related nutritional and hormonal disturbances, such as hypercortisolemia, further worsen bone health (4, 5).

Demonstrating the marked detrimental bone effects, 44% of women with FHA have low BMD, and 10-25% have lumbar spine (LS) BMD *Z*-scores ≤−2 compared with 0-1% of healthy women (4, 5). Indeed, fracture risk is 2-7 times higher than in age and sex-matched healthy women (6, 7). Thus, to restore menses and recover bone health in women with FHA, reversal of the relative energy deficiency state and/or stress is key. This is ideally achieved by weight regain, rationalizing exercise routines, and/or reducing psychological stress (1, 7).

However, menses restoration through lifestyle modification is frequently not successful, especially within the necessary timeframe to preserve bone health (8). Indeed, despite one year of psychological and dietetic interventions, up to 68% of women with FHA do not recover menses (8). In the long-term, approximately 30% of women remain amenorrheic after nine years of follow-up (9). Delays in restoring physiological menses (and therefore estrogen), if at all restored, lead to adverse bone sequelae (10-12). Consequently, several pharmacological interventions have been studied to preserve BMD in women with persistent FHA. These include hormone-based interventions, such as hormone replacement therapy (HRT) containing physiological estrogen doses, or the combined oral contraceptive pill (COCP) containing supraphysiologic synthetic estrogen. Non-hormonal interventions, including teriparatide, a potent osteoanabolic agent, and recombinant human insulin-like growth factor 1 (rhIGF-1) have also been investigated (7). Regarding recombinant human insulin-like growth factor-1 (rhIGF-1) therapy, this targets the marked insulin-like growth factor-1 (IGF-1) deficiency seen in anorexia nervosa (AN)-related FHA, where circulating levels are approximately 50% lower than in healthy women due to growth hormone resistance (13). As IGF-1 promotes osteoblast activity and collagen synthesis, restoration through exogenous administration of rhIGF-1 in women with AN-related FHA may enhance bone formation and thereby improve BMD in this setting (14-17).

Selection of bone-directed therapy in FHA is typically guided by the outcome of non-pharmacological interventions and fracture risk. International guidelines for FHA recommend *transdermal* HRT as first-line pharmacotherapy to promote bone health in most women who have not had a return of menses after a trial of nutritional, psychological, and exercise modification interventions (1). Nevertheless, the recommendation for the transdermal route is made with 'very low' certainty, as it is based on only two randomized-controlled trials (RCTs) examining the effects of HRT on bone (18, 19). In addition, guidelines advise against COCP-use with 'low' level of evidence, citing the lack of prospective studies investigating COCP-use in FHA (1). COCP-use is of paramount clinical importance as recent data revealed that 25% of women with AN-related FHA receive the COCP for osteopenia/osteoporosis, rather than HRT (20). With regard to patient stratification and treatment selection, anabolic agents such as teriparatide are occasionally considered, although generally off-license, in premenopausal women with very low BMD and/or fractures and/or delayed fracture healing. Therefore, teriparatide is generally reserved only for selected cases after careful consideration of risks and benefits, and is typically short-term (≤2 years) (1). Additionally, international guidelines for FHA advise against the use of antiresorptive agents, such as bisphosphonates and denosumab, in women of reproductive age, reflecting limited efficacy evidence and safety concerns (1). Indeed, bisphosphonates have a prolonged skeletal half-life and unclear teratogenic or neonatal risks (21), while denosumab has been associated with adverse neonatal outcomes in preclinical models (22), rendering both potentially unsuitable for this population (7). Therefore, there is a clear need to accumulate evidence to guide clinical recommendations in this common reproductive disorder.

Herein, we conducted the first systematic review and network meta-analysis (NMA) to address this knowledge gap by synthesizing the evidence for all available pharmacological interventions for BMD in women with FHA and provide direct and indirect comparisons between these interventions.

Methods

Reporting methods and protocol

This systematic review and NMA were prospectively registered on PROSPERO (ref: CRD42024576872) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23).

Literature sources and search

The search strategy was devised in collaboration with an independent information specialist (A.M.) and peer-reviewed by two investigators (A.E., K.T.). Medline (Ovid), Embase (Ovid), Emcare (Ovid), and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for completed published RCTs, with searches performed until 20 September 2025. The International Standard Randomized Controlled Trial Number and ClinicalTrials.gov databases were searched for unpublished studies. Further details are provided in the Appendix, including a full search strategy for Ovid Medline (Table S1) (24). The search strategy was adapted for Embase (Ovid), Emcare (Ovid), and Cochrane Central Register of Controlled Trials (CENTRAL).

Article screening & selection criteria

Two reviewers (A.E., K.T.) independently performed title, abstract, and full-text screening of the articles retrieved through systematic literature searches. Discrepancies were resolved through discussion with A.N.C. (independent of the initial screening). Studies not conforming to all prespecified inclusion

criteria or meeting any exclusion criteria (Appendix) (24) were excluded.

Outcome measures

The primary outcome was lumbar spine (LS) BMD determined by Dual Energy X-Ray Absorptiometry (DXA). Secondary outcomes were femoral neck (FN) and total hip (TH) BMD. Further details on outcome measures are provided in the Appendix (24).

Data extraction

Two reviewers (A.E., K.T.) independently extracted data.

Quality appraisal

To evaluate the confidence in the NMA results, the validated "Confidence in Network Meta-Analysis" (CINeMA) framework was adopted. The Cochrane risk-of-bias tool for RCTs (RoB) was used to assess risk-of-bias (Appendix) (24, 25). Publication bias was assessed using the Egger's test only when ≥10 studies evaluated an outcome (26).

Data analysis

Statistical analyses were conducted according to Cochrane Handbook recommendations. When standard errors of the mean were provided, they were used to calculate standard deviations (27). Regarding the meta-analyses, both pairwise analyses and NMA were conducted using standardized mean difference (SMD), with different bone densities serving as dependent outcomes.

For the pairwise quantitative synthesis, a random-effects model was employed, using Review Manager software, version 7.12.0 (The Nordic Cochrane Center, Denmark) (28). Heterogeneity was assessed by Cochran's Q, I^2 (27). The NMA and network plots were performed using Stata version 16.0 (StataCorp LLC Statistics/Data Analysis StataCorp, USA) (29). NMA within the frequentist framework using the mvmeta package was conducted (30).

Global inconsistency across different treatment comparisons in the network was assessed using a design-by-treatment model based on the *P*-value (31). Potential inconsistencies between direct and indirect evidence were further evaluated with the loop-specific approach, and local inconsistencies were identified using the node-splitting technique (32).

Subgroup analysis

We subsequently conducted a prespecified subgroup analysis assessing the effects of pharmacological interventions in distinct FHA subgroups, specifically women with AN-related FHA and those with exercise-related FHA.

Network meta-regression

Using the web-based MetaInsight tool (33), post-hoc network meta-regression analyses were performed to examine the influence of age, body mass index, duration of amenorrhea, baseline BMD at each skeletal site, and intervention duration on LS BMD, FN BMD, and TH BMD.

Sensitivity analysis

A prespecified network sensitivity analysis was conducted for the primary outcome (LS BMD) to assess the impact of studies with low and moderate risk of bias, excluding studies with high risk of bias.

Further details on data extraction, quality appraisal, subgroup analysis, as well as clinical translation of results are provided in the Appendix (24).

Results

1386 records were identified during the systematic literature search, of which 349 duplicate records and 998 records not meeting eligibility criteria following title/abstract screening were excluded (PRISMA flow diagram, Fig. 1). Subsequently, 26 records were excluded as not meeting eligibility criteria following full-text screening (Table S2) (24). Therefore, 13 eligible RCTs (published 1997-2019) were included. Data for LS BMD (primary outcome) were available for 897 participant observations across all pharmacotherapy comparisons, corresponding to 692 unique women. Not all the studies included reported FN or TH BMD, resulting in 370 and 750 participant observations across comparisons, corresponding to 282 and 557 unique women respectively for these secondary outcomes; 897 participant observations included for the primary outcome in this NMA exceeds the sample size in the largest RCT to-date on this topic (150 women), adding strength to this study (34).

Ten different pharmacological interventions were identified (Table S3) (24). Calcium/vitamin D supplementation occurred in the majority of studies, with doses ranging 500-1500 mg for calcium carbonate and 400-800 IU for vitamin D, but was unreported in five studies (19, 34-37) (Table S3) (24). Vitamin D levels varied from 27.1-40.4 ng/mL (67.8-101.0 nmol/L) across the included studies, indicating generally sufficient vitamin D status (18, 38-40). Furthermore, the duration of amenorrhea was variable. All but one study ranged from 6-30 months, with the study by Gibson reporting a longer duration of 7 years (Table S3) (24). Intervention duration was 12-24 months for *oral* HRT studies, 12-18 months for *transdermal* HRT, and 9-24 months for COCP (Table S3) (24). Only one study assessed the impact of pharmacological interventions on clinical fractures and found no significant difference in stress fracture incidence between the COCP and the control group (34).

With the exception of the study by Fazeli et al (38), which enrolled women with a mean age of 47 years, all other trials recruited adolescent and young adult women, with mean participant ages not exceeding 30 years (Table S3) (24). Baseline Z-scores across the included studies ranged from −2.0 to −0.6 at the lumbar spine, −1.8 to 0.1 at the femoral neck, and −1.0 to 0.3 at the total hip, indicating bone mineral density

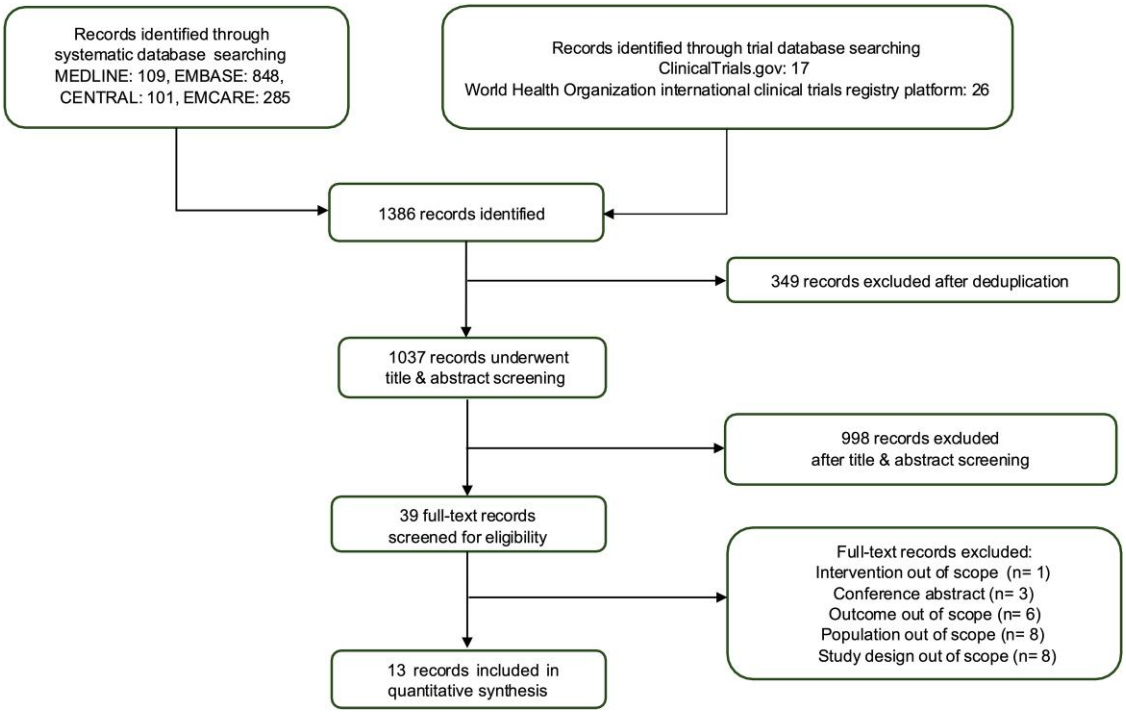

Figure 1 PRISMA flow diagram. Study selection process for the systematic review and network meta-analysis.

within the expected range, albeit below the expected mean (Table S3) (24). By contrast, Fazeli et al investigated an older cohort of premenopausal women (mean age: 47 years), and bone density in this study was expressed as T-scores rather than *Z*-scores (38). In this study, women receiving teriparatide had mean baseline T-scores of −2.6 at the lumbar spine, −2.3 at the femoral neck, and −1.9 at the total hip, indicating lower bone density at baseline compared with the younger cohorts enrolled in the other trials (38).

In the study by Misra et al, lumbar spine Z-scores declined only slightly in women treated with *transdermal* HRT, by 0.03, whereas untreated women with FHA showed a significantly greater reduction of 0.24 at the lumbar spine within 18 months (18). At the total hip, Z-scores decreased by 0.18 in women treated with *transdermal* HRT, compared with a significantly larger decline of 0.33 in untreated women (18). Furthermore, Ackerman et al showed that lumbar spine Z-scores increased by 0.13 at 12 months in women receiving *transdermal* HRT, whereas the COCP and control groups showed small declines of 0.04 and 0.09, respectively (39). The improvement with *transdermal* HRT was significantly greater than the changes seen with COCP and with control. At the femoral neck, Z-scores increased by 0.33 with *transdermal* HRT, compared with smaller gains of 0.10 with COCP and 0.08 with control. Here, too, *transdermal* HRT produced significantly greater improvements than both COCP and control. By contrast, total hip *Z*-scores showed minimal change, rising by 0.05 with *transdermal* HRT and falling by 0.14 and 0.07 in the COCP and control groups, respectively. At this site, HRT was only significantly better than COCP, with no significant difference compared to control. Additionally, in the study by Golden et al, lumbar spine and femoral neck Z-scores remained stable following alendronate treatment for approximately 12 months (41). Taken together, these findings indicate that transdermal HRT led to greater improvements compared with control or COCP at all skeletal sites in the individual studies, aligning with the current network meta-analysis.

Across all pharmacotherapies, adverse events were generally mild and consistent with expected safety profiles. The COCP and *transdermal* HRT were associated with irregular or withdrawal bleeding, occurring in 19-100% and up to 23% of participants, respectively. The COCP was also associated with headache, mood changes, breast tenderness, and abdominal discomfort, with these side effects leading to treatment discontinuation in up to 7% of participants. Teriparatide led to mild adverse events, such as injection-site reactions, none of which resulted in treatment discontinuation.

Pairwise meta-analysis was performed for LS, FN, and TH BMD. Pairwise meta-analysis outcomes are provided in Fig. S1 (24).

NMA outputs were generated as SMDs for all outcomes and then back-transformed to mean differences (MDs) to provide intuitive clinical estimates. NMA outcomes are reported both as standardized mean differences (SMDs, 95% CI) and mean differences (MDs, 95% CI) for clinical interpretation.

Main outcomes

NMA for LS BMD (primary outcome)

The network plot for LS BMD had a hub-and-spoke pattern, with control serving as the common comparator for direct comparisons with most interventions (Fig. S2A) (24). Compared with control, *transdermal* HRT was superior in increasing LS BMD (SMD: 0.34 [0.03, 0.64]; MD 0.041 g/cm^2 [0.004, 0.077]) (Fig. 2A and 2B). By contrast, no significant difference was observed for *oral* HRT (SMD: 0.13 [−0.47, 0.72]; MD: 0.016 g/cm^2 [−0.056, 0.086])

A

COCP										
-0.26 (-0.62, 0.09)	Transdermal HRT									
-1.75 (-2.83, -0.66)	**-1.48 (-2.59, -0.38)**	Teriparatide								
-0.39 (-1.27, 0.49)	-0.13 (-1.03, 0.77)	1.35 (0.00, 2.71)	Metreleptin							
-0.68 (-1.33, -0.04)	-0.42 (-1.13, 0.29)	1.06 (-0.18, 2.30)	-0.29 (-1.36, 0.78)	COCP+rhIGF-1						
-0.27 (-0.90, 0.36)	-0.01 (-0.70, 0.69)	**1.48 (0.24, 2.71)**	0.12 (-0.94, 1.18)	0.41 (-0.31, 1.13)	rhIGF-1					
0.07 (-0.66, 0.80)	0.34 (-0.42, 1.09)	**1.82 (0.55, 3.09)**	0.46 (-0.63, 1.56)	0.76 (-0.19, 1.71)	0.34 (-0.60, 1.28)	Alendronate				
-0.14 (-0.64, 0.35)	0.12 (-0.42, 0.65)	**1.60 (0.45, 2.75)**	0.25 (-0.71, 1.20)	0.54 (-0.24, 1.32)	0.13 (-0.65, 0.90)	-0.22 (-1.04, 0.60)	COCP+DHEAS			
-0.06 (-0.69, 0.58)	0.21 (-0.46, 0.88)	**1.69 (0.48, 2.91)**	0.34 (-0.70, 1.37)	0.63 (-0.25, 1.51)	0.21 (-0.65, 1.08)	-0.13 (-1.04, 0.79)	0.09 (-0.65, 0.83)	Oral HRT		
0.07 (-0.15, 0.30)	**0.34 (0.03, 0.64)**	**1.82 (0.76, 2.88)**	0.46 (-0.39, 1.31)	**0.76 (0.11, 1.40)**	0.34 (-0.29, 0.98)	0.00 (-0.69, 0.69)	0.22 (-0.22, 0.66)	0.13 (-0.47, 0.72)	Control	
0.71 (-0.19, 1.61)	**0.97 (0.04, 1.90)**	**2.46 (1.08, 3.84)**	1.10 (-0.12, 2.33)	**1.39 (0.31, 2.48)**	0.98 (-0.10, 2.06)	0.64 (-0.49, 1.76)	0.85 (-0.13, 1.84)	0.76 (-0.30, 1.83)	0.64 (-0.25, 1.52)	Medroxyprogesterone

B

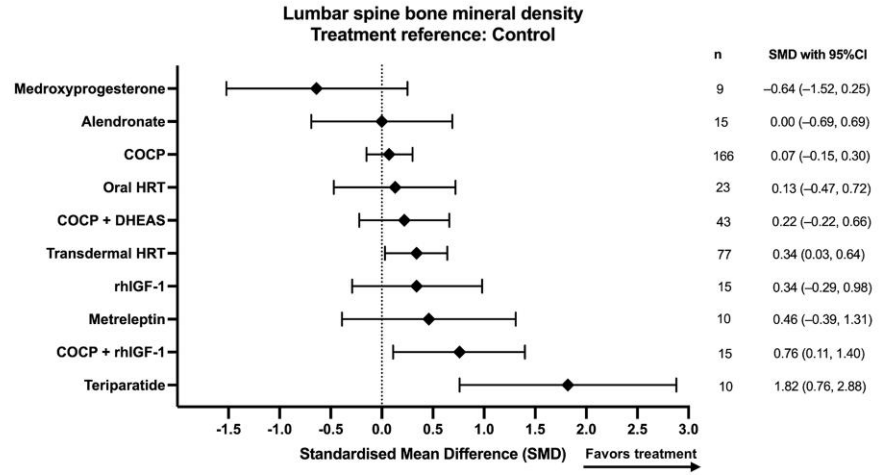

Figure 2 Network league illustrating standardized mean differences (SMDs) for lumbar spine bone mineral density results (primary outcome) (A). Between-intervention comparisons should be read from left to right. Effect size estimates for each intervention comparison are situated at the intersection between the column and row defining each intervention. Statistically significant results are shown in bold within shaded boxes. Network meta-analysis for lumbar spine bone mineral density (B). COCP, combined oral contraceptive pill; DHEAS, dehydroepiandrosterone; HRT, hormone replacement therapy; MPG, medroxyprogesterone; rhIGF-1, recombinant human insulin-like growth factor-1.

or for COCP (SMD: 0.07 [−0.15, 0.30]; MD: 0.084 g/cm^2 [−0.018, 0.036]).

However, teriparatide was superior to *transdermal* HRT (SMD: 1.48 [0.38, 2.59]; MD: 0.178 g/cm^2 [0.046, 0.311]), to *oral* HRT (SMD: 1.69 [0.48, 2.91]; MD: 0.203 g/cm^2 [0.058, 0.349]), and to COCP (SMD: 1.75 [0.66, 2.83]; MD: 0.210 g/cm^2 [0.079, 0.340]). Additionally, teriparatide was superior to recombinant human IGF-1 (SMD: 1.48 [0.24, 2.71]; MD 0.178 g/cm^2 [0.029, 0.325]), alendronate (SMD: 1.82 [0.55, 3.09]; MD: 0.218 g/cm^2 [0.066, 0.371]), and the COCP + dehydroepiandrosterone (DHEAS) combination (SMD: 1.60 [0.45, 2.75]; MD: 0.192 g/cm^2 [0.054, 0.330]). Finally, the COCP + rhIGF-1 combination was superior to control (SMD: 0.76 [0.11, 1.40]; MD: 0.091 g/cm^2 [0.013, 0.168]) and to medroxyprogesterone (SMD: 1.39 [0.31, 2.48]; MD: 0.167 g/cm^2 [0.037, 0.298]).

NMA for FN and TH BMD (secondary outcomes)

The network plots for FN and TH BMD demonstrated a hub-and-spoke pattern (Fig. S2B and S2C) (24). Compared with control, *transdermal* HRT was superior in increasing FN BMD (SMD: 0.57 [0.04, 1.10]; MD: 0.068 g/cm^2 [0.005, 0.132]) (Fig. 3A and 3B). By contrast, NMA results for TH BMD displayed no significant differences between any of the comparator interventions (Fig. S3A and S3B) (24).

Subgroup analysis

Subgroup analysis in exercise-related FHA demonstrated that none of the interventions exerted any significant impact on LS BMD. In women with anorexia-related FHA, teriparatide was the only intervention that resulted in a significantly greater improvement in LS BMD compared with control (SMD: 1.82 [0.76-2.88]; MD: 0.22 g/cm^2 [0.09-0.35]). Further details of the subgroup analysis are presented in Appendix (24).

Network meta-regression analyses

None of the evaluated covariates (age, BMI, duration of amenorrhea, baseline BMD at the corresponding skeletal site, or intervention duration) significantly modified treatment effects on LS, FN, and TH BMD, although due to separation of subtypes,

A

COCP						
-0.52 (-1.05, 0.01)	**Transdermal HRT**					
-0.38 (-1.30, 0.54)	0.14 (-0.88, 1.15)	**Teriparatide**				
-0.08 (-0.83, 0.68)	0.44 (-0.43, 1.31)	0.30 (-0.81, 1.42)	**Alendronate**			
0.07 (-0.86, 0.99)	0.59 (-0.44, 1.61)	0.45 (-0.79, 1.68)	0.14 (-0.97, 1.26)	**Oral HRT**		
0.05 (-0.25, 0.35)	**0.57 (0.04, 1.10)**	0.43 (-0.44, 1.30)	0.13 (-0.57, 0.82)	-0.02 (-0.89 ,0.86)	**Control**	
-0.14 (-1.00, 0.72)	0.37 (-0.60, 1.35)	0.24 (-0.97, 1.45)	-0.07 (-1.16, 1.02)	-0.21 (-1.43, 1.00)	-0.19 (-1.03 ,0.65)	**Medroxyprogesterone**

B

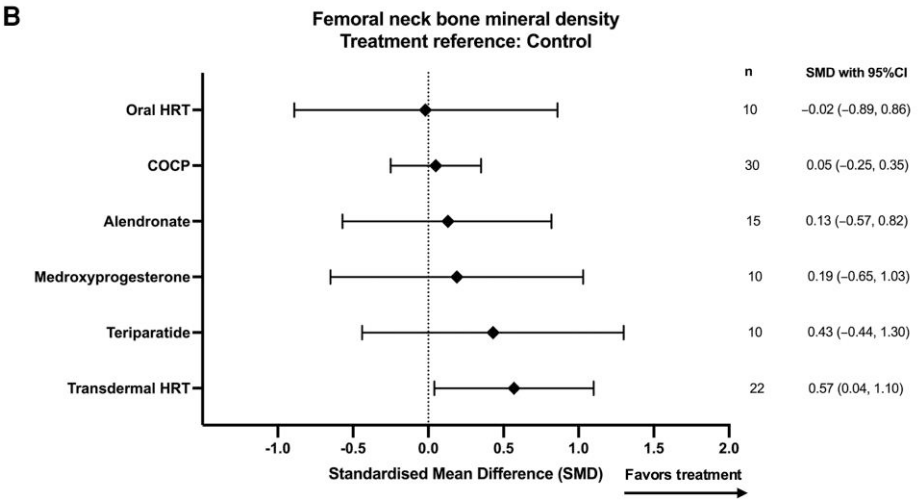

Figure 3 Network league reporting standardized mean differences (SMDs) for femoral neck results (A). Between-intervention comparisons should be read from left to right. Effect size estimates for each intervention comparison are situated at the intersection between the column and row defining each intervention. Statistically significant results are shown in bold within shaded boxes. (B) Network meta-analysis for femoral neck bone mineral density (B). COCP, combined oral contraceptive pill; HRT, hormone replacement therapy; MPG, medroxyprogesterone.

the statistical power was likely too low. Further details of network meta-regression analyses are presented in Appendix (24).

Global and local inconsistency

We observed no global or local inconsistencies in the studies assessed for most compared intervention pairs ($P > .05$) (Tables S4 and S5) (24). The only exception was the comparison between COCP and control ($P = .017$), indicating potential inconsistency between direct and indirect evidence for this pair, therefore warranting cautious interpretation.

Quality of evidence

Low within-study risk of bias was observed for randomization, blinding of outcome assessors, incomplete outcome data, selective reporting, outcome measurement, deviation from planned intervention, and other biases (Figs. S4 and S5) (24). To evaluate the quality of evidence for each comparison, we followed the CINeMA approach. Here, most of the intervention comparisons received a judgement of 'low' or 'very low' confidence, mainly due to imprecision (Tables S6-S8) (24).

Further details of publication bias and sensitivity analysis are presented in Appendix (24).

Discussion

FHA reflects an estrogen and often nutritionally deficient state, disrupting normal skeletal homeostasis with marked and frequently long-lasting detrimental effects on bone health (7). International guidelines advocate initiation of hormonal interventions if amenorrhea persists despite 6-12 months of nutritional, exercise-related, and psychological interventions if there is low BMD (1). Despite these recommendations, underlying large-scale evidence as to whether the COCP, *oral* HRT, or *transdermal* HRT has greater benefit on bone density is currently lacking, as well as head-to-head trials comparing hormonal and non-hormonal interventions. To our knowledge, this is the first NMA evaluating this clinical conundrum by providing direct and indirect comparisons between available pharmacological interventions for women with persistent FHA.

This study demonstrates that *transdermal* HRT is superior to control in increasing LS BMD (pairwise and NMA) and FN BMD (NMA), which is consistent with smaller-scale trials (42-44). By contrast, neither *oral* HRT nor COCP showed any significant difference compared to control. Of note, two studies reported a significant improvement in LS BMD with COCP-use compared with control (36, 37). However, one of these studies (Castelo-Branco et al) was judged to be at high risk of bias (37), with unclear randomization and allocation concealment, and a lack of blinding.

The study also did not account for key lifestyle factors such as physical activity or vitamin D status, which may have affected outcomes. The second study (Hergenroeder et al) employed a small sample size ($n = 5$ for COCP and control, respectively) and doses of administered vitamin D were not reported. These limitations might explain the discrepancy between the results of these two studies and the meta-analytic evidence, including a study by Aalberg et al (45), showing no benefit of the COCP on BMD.

There are several possible explanations as to why *transdermal* HRT, unlike *oral* HRT and COCP, performs better on BMD than control. Oral estrogens (as in *oral* HRT and COCP) undergo first-pass metabolism, which suppresses bone-anabolic IGF-1 production and increases sex hormone-binding globulin (SHBG), leading to a reduction in free (biologically-available) estrogen. By contrast, transdermal delivery of estrogens in HRT does not suppress IGF-1 or free estrogen, both of which are important for bone metabolism (46-48). Indeed, IGF-1 has established anabolic effects on bone through increases in osteoblast activity and collagen synthesis and is approximately 50% lower in women with AN, compared with normal-weight women (13). Therefore, further IGF-1 suppression from an already low level can further compromise BMD (13). Furthermore, high SHBG levels seen with COCP reduce bioavailable estrogens crucial for bone maintenance (49).

An additional explanation is that the COCP typically contains synthetic estrogen derivatives (eg, ethinylestradiol), which may be less favorable on bone compared with *oral* HRT containing more physiologic estrogens (eg, estradiol valerate) (1, 50). Also, COCP regimens typically include a pill-free week each month, with no estrogen administered, whereas HRT provides continuous estrogens (1, 50).

Collectively, these factors may explain the superior bone-related effects observed with *transdermal* over *oral* HRT and COCP. These findings are potentially immediately practice-changing given that recent data demonstrate that 25% of women with AN-related FHA receive the COCP for osteopenia/osteoporosis, as well as the findings from our patient and public involvement and engagement (PPIE) cohort (Appendix) (20, 24). These results could thus support evidence-based practice change favoring *transdermal* HRT over the COCP for women with FHA.

Regarding bone-specific interventions, teriparatide is superior to all interventions in lumbar spine improving BMD, including *transdermal* HRT. Despite this, HRT may still be preferable for most women with FHA, given its additional clinical benefits (eg, endometrial and cardiovascular health, and quality of life) (1, 51). Furthermore, teriparatide is generally reserved for adult FHA cases as an option in the setting of delayed fracture healing and very low BMD (1). Indeed, teriparatide cessation after two years would likely lead to loss of the BMD gained whilst on treatment if menses are not restored (52, 53). By comparison, HRT can be used for extended timeframes, offering longer-term bone protection, potentially for many years.

Interestingly, alendronate was not superior to control for BMD gain at any site. This was anticipated, as the only study in adolescent women with AN found no difference in BMD gain between alendronate and control (41). However, in the same study, subgroup analysis showed weight-restored women (51.7% of the cohort) had significant LS and FN BMD gains with alendronate, compared to control. This highlights the confounding role of weight restoration as a key determinant of BMD recovery, independent of pharmacological intervention. Indeed, this confounding effect is likely relevant not only to alendronate but across interventions evaluated in this population, since nutritional and hormonal normalization are fundamental prerequisites for bone accrual (1, 7, 50). Furthermore, alendronate and other bisphosphonates are frequently used in FHA, and so this adds to the weight of evidence against their use, coupled with potential perinatal risks and the potential blunting of bone recovery from remodeling suppression (54).

The amenorrheic patients included in the NMA met the standard diagnostic criteria for FHA, with an absence of menstrual cycles for >3-months (1). However, the definition of oligomenorrhea was less consistent across studies, ranging from <6 to 4-9 cycles/year (Table S3) (24), although still meeting the standard criteria of ≥45 days between cycles, confirming a homogeneous population in amenorrhea classification (1).

Notably, women with AN display lower BMD and greater bone microarchitecture impairment at all skeletal sites when compared to normal-weight athletes with oligomenorrhea and normal-weight eumenorrheic women (4). Therefore, we performed a subgroup analysis exclusively in athletes with FHA, demonstrating that none of the interventions exerted any significant impact on LS BMD. By contrast, in the subgroup of women with anorexia-related FHA, teriparatide demonstrated a significantly greater improvement in LS BMD compared with control. Therefore, further studies are warranted, examining potential differential effects of available interventions depending on the subtype of FHA.

A key systematic review and (non-network) meta-analysis by Aalberg evaluated the effect of estrogen therapy (COCP and HRT) on LS BMD in women with FHA but did not separate out the effects of different administration routes (45). Pooled data from nine RCTs ($n = 770$) demonstrated no significant difference in LS BMD between women receiving estrogen-based therapies compared to controls. By contrast, the current study demonstrates that *transdermal* HRT is superior to control in improving both LS and FN BMD. Several factors may explain this difference. Firstly, the current NMA combines direct and indirect evidence collected from a larger number of studies (thirteen studies, contributing 897 participant observations across all pharmacotherapy comparisons), compared to nine studies in Aalberg et al. Secondly, a traditional meta-analysis only provides direct but not indirect comparisons between interventions, unlike NMA. Thirdly, Aalberg pooled women who were on HRT and COCP, which may have diluted any beneficial effect of HRT on LS BMD (45).

Our study has several strengths. The protocol was prospectively registered in PROSPERO with prespecified eligibility criteria selected to ensure an exclusive FHA cohort, rather than mixed with amenorrhea for other reasons (ie, premature ovarian insufficiency). Notably, given that FHA is a diagnosis of exclusion, the studies included in our meta-analysis recruited amenorrheic and oligomenorrheic women specifically in the context of relative energy deficiency (eg, AN-related or exercise-related oligomenorrhea). This is distinct from other conditions causing menstrual disturbance, such as polycystic ovary syndrome (PCOS), which, unlike FHA, is not classically characterized by hypoestrogenism (55). Consistent with this, in our pairwise meta-analyses for LS BMD (primary outcome) comparing *transdermal*

HRT vs control, *oral* HRT vs control, and COCP vs control, heterogeneity was absent ($I^2 = 0\%$). In addition, we conducted pairwise comparisons and NMA using up-to-date methods, enabling direct and indirect comparisons with prespecified risk of bias and evidence quality assessments. Finally, we conducted PPIE sessions to better understand the views of women with FHA, who highlighted the importance of raising awareness and continuing research to determine the most effective pharmacological intervention (reported in Appendix) (24).

Certain limitations must also be considered. This NMA included women with both AN-related and exercise-related FHA. Although both subtypes share hypoestrogenism as the key driver for adverse bone health, these groups may differ in their underlying nutritional and metabolic status, including variations in micronutrient availability and energy expenditure, which could influence treatment response. However, detailed reporting of participants' nutritional status was absent in most included studies. To address this potential source of heterogeneity, we first conducted a network meta-regression using body mass index as the best-available proxy for nutritional status, which showed no significant effect on LS BMD, FN BMD, and TH BMD (Appendix) (24). We further explored this by performing subgroup analyses by FHA subtype. In exercise-related FHA, *transdermal* HRT did not significantly improve lumbar spine BMD. However, this finding was based on a single study and hence should be interpreted with caution. By contrast, all participants receiving teriparatide had AN-related FHA, so no teriparatide study was included in the exercise-related subgroup. Within the AN-related group, teriparatide continued to show a beneficial effect on LS BMD. Further RCTs examining FHA resulting from different behaviors (eating disorders/exercise) separately are required to more clearly delineate the respective benefits of pharmacotherapies. However, it is also worth considering that eating disorders and excessive exercise frequently overlap, with approximately half of women with AN engaging in compulsive or excessive exercise behaviors, and so combining subtypes of FHA as commonly done in the literature provides important clinical evidence (56). Furthermore, there were inherent differences in the duration of amenorrhea prior to assessment in the studies, including those that investigated different HRT formulations (Table S3) (24). Notably, Gibson included patients with FHA for ~7 years prior to *oral* HRT (35), while Warren did not specify FHA duration prior to commencing *oral* HRT (19). Conversely, studies of *transdermal* HRT recruited patients with FHA for ~12 months before intervention (18, 39). However, network meta-regression analysis did not show that duration of amenorrhea significantly influenced treatment effects on LS, FN, and TH BMD. Furthermore, all but one of the included studies (Fazeli et al) recruited adolescent and young adult women (mean ages ≤30 years) (38). This age range coincides with the period of peak bone mass accrual, which typically occurs during the late teens to the third decade of life (57). By contrast, Fazeli et al examined the effects of teriparatide in older premenopausal women with FHA (mean age 47 years). Although variation in age could have influenced bone metabolism independently of FHA, such age ranges are common in osteoporosis intervention studies (58, 59), and importantly, network meta-regression analysis did not show that age significantly influenced treatment effects on LS, FN, and TH BMD (Appendix) (24). Also, in studies of women taking the COCP or HRT, blinding may have been compromised as participants could develop breakthrough bleeding, potentially unmasking the intervention, and in some studies, no intervention was used as the comparator (rather than placebo). However, as BMD is an objective measure, this risk of bias is likely to be limited. Another limitation is the use of different bone densitometry machines across studies. For example, Warren used a DP3 Dual Photon Spine/Femur Scanner and an SP2 Single Photon Scanner (19). Gibson, Misra, and Ackerman used Hologic QDR1000W densitometer (35), Hologic 4500A densitometer (35), and Hologic QDR-Discovery A (18), respectively. However, all individual studies were completed on the same machine. Additionally, there was variability in the formulation and dosage of calcium and vitamin D supplementation across studies, and several did not specify whether women received vitamin D or calcium. Nevertheless, this is unlikely to affect the conclusions of this NMA, as most studies (including the *transdermal* HRT and teriparatide trials) ensured adequate supplementation. Furthermore, vitamin D levels were reported in eight of the thirteen included studies, and levels were sufficient. This is important as calcium and vitamin D are key for bone mineralization, and a prerequisite for the optimal effectiveness of bone-directed pharmacotherapies (60).

This NMA evaluated BMD and not the key clinical outcome of fractures (7). The effect of pharmacological interventions on clinical fractures was assessed in a single trial (34). In the study by Cobb et al, 18 runners experienced stress fractures (six in the COCP group and twelve in the control group) (34). Although the study demonstrated a 43% lower incidence of stress fractures among COCP users, this difference did not reach statistical significance, likely due to limited statistical power (34). The scarcity of RCTs assessing fractures as a primary outcome likely reflects the low incidence of fractures in women with FHA compared with postmenopausal women. Consequently, decades of follow-up and substantially larger sample sizes would be required to accrue sufficient fracture events to adequately power an RCT with fractures as the main outcome in FHA. Finally, although several pharmacological intervention comparisons were rated as having lower confidence, this analysis provides the most comprehensive synthesis to date and supports the use of HRT, rather than the COCP, as the preferred option for improving BMD in women with FHA based on current evidence. However, it is important that the incorporation of this evidence into guidelines and clinical practice takes into account the aforementioned limitations of current evidence during the routine grading of guideline recommendations. Although these recommendations must assess the best-available evidence, such as in the current study, they should also highlight the need for further studies in this important area of women's health.

Conclusion

This is the largest systematic review and first NMA investigating the comparative efficacy of available pharmacological interventions to protect BMD in women with persistent FHA. We demonstrate that *transdermal* HRT exerts a clinically significant positive effect on LS and FN BMD in women with persistent FHA. Similarly, we show that teriparatide exerts a clinically significant positive effect on LS BMD. By contrast, *oral* HRT and COCP did not exert any significant effects on BMD. Collectively, these findings are of

clinical importance as they provide the largest evidence-base to-date for a preferred hormonal pharmacological intervention and route (namely *transdermal* HRT), as well as the effectiveness of teriparatide for BMD in one of the commonest reproductive disorders encountered in routine clinical practice, and so can inform future guidelines.

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Author contributions

A.N.C. and A.E. conceived and designed the study. A.E. and K.T. collected and curated the data. A.M. and A.E. designed and run the literature search. A.E. and K.T. performed title and abstract screening, full-text screening and statistical analysis. A.E. and E.M. conducted patient and public involvement activity. A.E. wrote the first draft of the manuscript, with further input from all authors. A.N.C. supervised the complete work. All authors critically revised the manuscript for important intellectual content. All authors had full access to all the data in the study and verified the underlying data. All authors had final responsibility for the decision to submit for publication.

Disclosures

A.A. has conducted consultancy work for Myovant Sciences Ltd outside the submitted work. W.S.D. has conducted consultancy work for AbCellera, PostEra, KaNDy Therapeutics Ltd, and Myovant Sciences Ltd outside the submitted work. A.N.C. has received non-promotional educational speaking honoraria and meeting attendance support from UCB, Amgen, and Astellas outside the submitted work. The other authors declare no conflict of interest.

Data availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

Ethical approval

This systematic review was prospectively registered in PROSPERO CRD42024576872 and did not require additional ethical approval as only published datasets were used.

References

1. Gordon CM, Ackerman KE, Berga SL, et al. Functional hypothalamic amenorrhea: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102(5):1413-1439.
2. Shufelt CL, Torbati T, Dutra E. Hypothalamic amenorrhea and the long-term health consequences. *Semin Reprod Med*. 2017;35(3):256-262.
3. Phylactou M, Clarke SA, Patel B, et al. Clinical and biochemical discriminants between functional hypothalamic amenorrhoea (FHA) and polycystic ovary syndrome (PCOS). *Clin Endocrinol*. 2021;95(2):239-252.
4. Kandemir N, Slattery M, Ackerman KE, et al. Bone parameters in anorexia nervosa and athletic amenorrhea: comparison of two hypothalamic amenorrhea states. *J Clin Endocrinol Metab*. 2018;103(6):2392-2402.
5. Indirli R, Lanzi V, Mantovani G, Arosio M, Ferrante E. Bone health in functional hypothalamic amenorrhea: what the endocrinologist needs to know. *Front Endocrinol*. 2022;13:946695.
6. Rigotti NA, Neer RM, Skates SJ, Herzog DB, Nussbaum SR. The clinical course of osteoporosis in anorexia nervosa. A longitudinal study of cortical bone mass. *JAMA*. 1991;265(9):1133-1138.
7. Behary P, Comninos AN. Bone perspectives in functional hypothalamic amenorrhoea: an update and future avenues. *Front Endocrinol*. 2022;13:923791.
8. Pape J, Herbison AE, Leeners B. Recovery of menses after functional hypothalamic amenorrhoea: if, when and why. *Hum Reprod Update*. 2021;27(1):130-153.
9. Falsetti L, Gambera A, Barbetti L, Specchia C. Long-term follow-up of functional hypothalamic. *J Endocrinol Metab*. 2002;87(2):500-505.
10. Lucas AR, Melton LJ 3rd, Crowson CS, O'Fallon WM. Long-term fracture risk among women with anorexia nervosa: a population-based cohort study. *Mayo Clin Proc*. 1999;74(10):972-977.
11. Søeby M, Gribsholt SB, Clausen L, Richelsen B. Fracture risk in patients with anorexia nervosa over a 40-year period. *J bone Miner Res Off J Am Soc Bone Miner Res*. 2023;38(11):1586-1593.
12. Papageorgiou M, Dolan E, Elliott-Sale KJ, Sale C. Reduced energy availability: implications for bone health in physically active populations. *Eur J Nutr*. 2018;57(3):847-859.
13. Barrios V, Martín-Rivada Á, Guerra-Cantera S, et al. Reduction in pappalysin-2 levels and lower IGF-I bioavailability in female adolescents with anorexia nervosa. *J Clin Endocrinol Metab*. 2024;109(3):e920-e931.
14. Grinspoon SK, Baum HB, Peterson S, Klibanski A. Effects of rhIGF-I administration on bone turnover during short-term fasting. *J Clin Invest*. 1995;96(2):900-906.
15. Grinspoon SK, Friedman AJ, Miller KK, Lippman J, Olson WH, Warren MP. Effects of a triphasic combination oral contraceptive containing norgestimate/ethinyl estradiol on biochemical markers of bone metabolism in young women with osteopenia secondary to hypothalamic amenorrhea. *J Clin Endocrinol Metab*. 2003;88(8):3651-3656.
16. Locatelli V, Bianchi VE. Effect of GH/IGF-1 on bone metabolism and osteoporsosis. *Int J Endocrinol*. 2014;2014:235060.

17. Yuen KCJ. Growth hormone and bone: preclinical and clinical perspectives. *Endocr Pract*. 2025;31(9):1197-1206.
18. Misra M, Katzman D, Miller KK, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. *J Bone Miner Res*. 2011;26(10):2430-2438.
19. Warren MP, Brooks-Gunn J, Fox RP, et al. Persistent osteopenia in ballet dancers with amenorrhea and delayed menarche despite hormone therapy: a longitudinal study. *Fertil Steril*. 2003;80(2):398-404.
20. Davies HO. A local audit evaluating bone health in patients with functional hypothalamic amenorrhoea secondary to an eating disorder and a review of the application of hormone therapy in this clinical setting. *Post Reprod Heal*. 2024;30(3):182-189.
21. Sokal A, Elefant E, Leturcq T, Beghin D, Mariette X, Seror R. Pregnancy and newborn outcomes after exposure to bisphosphonates: a case-control study. *Osteoporos Int*. 2019;30(1):221-229.
22. Bussiere JL, Pyrah I, Boyce R, et al. Reproductive toxicity of denosumab in cynomolgus monkeys. *Reprod Toxicol*. 2013;42:27-40.
23. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-784.
24. Efthymiadis A, Tsikopoulos K, Mills EG, et al. 2025. Supplemental Data: "Pharmacological Interventions to Improve Bone Density in Functional Hypothalamic Amenorrhea: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials". *Figshare*. https://doi.org/10.6084/m9.figshare.30786146.
25. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
26. Page MJ, Higgins JP, Sterne JAC. Chapter 13: Assessing risk of bias due to missing evidence in a meta-analysis [last updated August 2024]. In: Higgins JP, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane*, 2024. cochrane.org/handbook
27. Higgins JP, Li T, Deeks JJ (editors). Chapter 6: Choosing effect measures and computing estimates of effect [last updated August 2023]. In: Higgins JP, ThomasJ, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane*, 2024. cochrane.org/handbook
28. Review Manager (RevMan) [Computer program]. Version 7.2.0. The Cochrane Collaboration, 2024. revman.cochrane.org
29. StataCorp. *Stata Statistical Software: Release 16*. StataCorp LLC. 2019.
30. White IR. Multivariate random-effects meta-regression: updates to mvmeta. *Stata J*. 2011;11(2):255-270.
31. Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol*. 2013;13(1):35.
32. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29(7-8):932-944.
33. Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: an interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. *Res Synth Methods*. 2019;10(4):569-581.
34. Cobb KL, Bachrach LK, Sowers M, et al. The effect of oral contraceptives on bone mass and stress fractures in female runners. *Med Sci Sports Exerc*. 2007;39(9):1464-1473.
35. Gibson JH, Mitchell A, Reeve J, Harries MG. Treatment of reduced bone mineral density in athletic amenorrhea: a pilot study. *Osteoporos Int*. 1999;10(4):284-289.
36. Hergenroeder AC, Smith EO, Shypailo R, Jones LA, Klish WJ, Ellis K. Bone mineral changes in young women with hypothalamic amenorrhea treated with oral contraceptives, medroxyprogesterone, or placebo over 12 months. *Am J Obstet Gynecol*. 1997;176(5):1017-1025.
37. Castelo-Branco C, Vicente JJ, Pons F, Martínez de Osaba MJ, Casals E, Vanrell JA. Bone mineral density in young, hypothalamic oligoamenorrheic women treated with oral contraceptives. *J Reprod Med*. 2001;46(10):875-879.
38. Fazeli PK, Wang IS, Miller KK, et al. Teriparatide increases bone formation and bone mineral density in adult women with anorexia nervosa. *J Clin Endocrinol Metab*. 2014;99(4):1322-1329.
39. Ackerman KE, Singhal V, Baskaran C, et al. Oestrogen replacement improves bone mineral density in oligo-amenorrhoeic athletes: a randomised clinical trial. *Br J Sports Med*. 2019;53(4):229-236.
40. Sienkiewicz E, Magkos F, Aronis KN, et al. Long-term metreleptin treatment increases bone mineral density and content at the lumbar spine of lean hypoleptinemic women. *Metabolism*. 2011;60(9):1211-1221.
41. Golden NH, Iglesias EA, Jacobson MS, et al. Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab*. 2005;90(6):3179-3185.
42. Resulaj M, Polineni S, Meenaghan E, Eddy K, Lee H, Fazeli PK. Transdermal estrogen in women with anorexia nervosa: an exploratory pilot study. *JBMR Plus*. 2020;4(1):e10251.
43. Nose-Ogura S, Yoshino O, Kanatani M, et al. Effect of transdermal estradiol therapy on bone mineral density of amenorrheic female athletes. *Scand J Med Sci Sports*. 2020;30(8):1379-1386.
44. Singhal V, Nimmala S, Slattery M, et al. Physiologic transdermal estradiol replacement mimics effects of endogenous estrogen on bone outcomes in hypoestrogenic women with anorexia nervosa. *Nutrients*. 2022;14(13):2557.
45. Aalberg K, Stavem K, Norheim F, Russell MB, Chaibi A. Effect of oral and transdermal oestrogen therapy on bone mineral density in functional hypothalamic amenorrhoea: a systematic review and meta-analysis. *BMJ Open Sport Exerc Med*. 2021;7(3):e001112.
46. Kam GY, Leung KC, Baxter RC, Ho KK. Estrogens exert route- and dose-dependent effects on insulin-like growth factor (IGF)-binding protein-3 and the acid-labile subunit of the IGF ternary complex. *J Clin Endocrinol Metab*. 2000;85(5):1918-1922.
47. Singhal V, Ackerman KE, Bose A, Flores LPT, Lee H, Misra M. Impact of route of estrogen administration on bone turnover markers in oligoamenorrheic athletes and its mediators. *J Clin Endocrinol Metab*. 2019;104(5):1449-1458.
48. Stomati M, Hartmann B, Spinetti A, et al. Effects of hormonal replacement therapy on plasma sex hormone-binding globulin, androgen and insulin-like growth factor-1 levels in postmenopausal women. *J Endocrinol Invest*. 1996;19(8):535-541.

49. Pugeat M, Crave JC, Tourniaire J, Forest MG. Clinical utility of sex hormone-binding globulin measurement. *Horm Res*. 1996;45(3-5):148-155.
50. Gordon CM. Clinical practice. Functional hypothalamic amenorrhea. *N Engl J Med*. 2010;363(4):365-371.
51. Webber L, Anderson RA, Davies M, Janse F, Vermeulen N. HRT for women with premature ovarian insufficiency: a comprehensive review. *Hum Reprod Open*. 2017;2017(2):hox007.
52. Cohen A, Kamanda-Kosseh M, Recker RR, et al. Bone density after teriparatide discontinuation in premenopausal idiopathic osteoporosis. *J Clin Endocrinol Metab*. 2015;100(11):4208-4214.
53. Leder BZ, Neer RM, Wyland JJ, Lee HW, Burnett-Bowie SAM, Finkelstein JS. Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. *J Clin Endocrinol Metab*. 2009;94(8):2915-2921.
54. Stathopoulos IP, Liakou CG, Katsalira A, et al. The use of bisphosphonates in women prior to or during pregnancy and lactation. *Hormones*. 2011;10(4):280-291.
55. Ott J, Robin G, Hager M, Dewailly D. Functional hypothalamic amenorrhoea and polycystic ovarian morphology: a narrative review about an intriguing association. *Hum Reprod Update*. 2025;31(1):64-79.
56. Campbell C, Greig X, Griffiths J, et al. The prevalence of excessive exercise in eating disorders: a systematic review and meta-analysis. *Eur Eat Disord Rev J Eat Disord Assoc*. 2025;33(5):1005-1016.
57. Baxter-Jones ADG, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass. *J Bone Miner Res*. 2011;26(8):1729-1739.
58. Winzenberg T, Oldenburg B, Frendin S, De Wit L, Riley M, Jones G. The effect on behavior and bone mineral density of individualized bone mineral density feedback and educational interventions in premenopausal women: a randomized controlled trial [NCT00273260]. *BMC Public Health*. 2006;6(1):12.
59. Wu F, Wills K, Laslett LL, et al. Individualized fracture risk feedback and long-term benefits after 10 years. *Am J Prev Med*. 2018;54(2):266-274.
60. Murshed M. Mechanism of bone mineralization. *Cold Spring Harb Perspect Med*. 2018;8(12):a031229.