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RESEARCH ARTICLE

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Chinese medicinal herbs for reducing endocrine therapy-induced side effects in patients with hormone receptor-positive breast cancer: a systematic review and meta-analysis

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ABSTRACT

Context: Chinese medicinal herbs (CMH) have been considered a potentially efficacious approach for patients with breast cancer that experience adverse effects from endocrine treatment.

Objective: To investigate the impact of CMH on endocrine therapy-induced side effects in patients with hormone receptor-positive (HR+) breast cancer.

Methods: Ten databases (e.g., PubMed, Web of Science, Cochrane Library, China National Knowledge Information Database and other databases) were searched up to 20 May 2022. The search terms included Chinese herb, breast cancer, endocrine therapy, clinical trial and their mesh terms. The study selection and data extraction were performed by two independent reviewers. The risk of bias was evaluated using the Cochrane risk of bias method.

Results: A total of 31 studies with 2288 patients were included. There were significant improvements in bone mineral density (BMD) [lumbar BMD (*MD* 0.08, 95% CI 0.07 to 0.09, $p < 0.00001$) and femoral neck BMD (*MD* 0.08, 95% CI 0.07 to 0.10, $p < 0.00001$)] and bone gal protein (BGP) (*MD* 0.24, 95% CI 0.17 to 0.31, $p < 0.00001$), with a significant reduction in triglycerides (MD −0.53, 95% CI −1.00 to −0.07, $p < 0.05$) and no effect on estradiol levels (MD 0.90, 95% CI −0.31 to 2.12, $p = 0.15$).

Conclusions: CMH combined with complementary therapy can moderately reduce endocrine therapy-induced side effects, including bone loss and dyslipidemia in patients with HR + breast cancer, revealing the potential role of CMH in treating (HR+) breast cancer. More high-quality RCTs are warranted to further validate the effectiveness and safety of CMH.

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Introduction

Breast cancer is the primary cause of cancer-related deaths among females. According to the Global Cancer Statistics 2020, breast cancer now exceeds lung malignancy as the most widely identified cancer in females, with an anticipated 2.3 million new cases (11.7%) and 0.69 million new deaths (6.9%) (Sung et al. 2021). In the United States, over 250,000 breast cancers are diagnosed annually (Siegel et al. 2020), and nearly 80% of breast cancers are hormone receptor-positive (HR+) (DeSantis et al. 2019). Most of these patients are dependent on endocrine therapy.

Endocrine therapies, such as aromatase inhibitors and tamoxifen, have been used as first-line therapy for patients with HR+ breast cancer (Johnston et al. 2009; Aggelis and Johnston 2019). Continuing tamoxifen for 10 years rather than 5 years has been reported to lead to further reductions in recurrence and mortality rates, especially after 10 years (Davies et al. 2013). Although endocrine therapy has been shown to benefit survival in patients with breast cancer, long-term adherence to endocrine therapy remains a major concern, partly due to the side effects of treatment, such as dyslipidemia, hot flashes, vaginal dryness, and musculoskeletal symptoms, which affect one's quality of life, social function, and adherence to treatment (Condorelli and Vaz-Luis 2018; Lee et al. 2020). Consequently, identifying new therapeutic methods to mitigate the adverse effects of endocrine therapy is critical.

Traditional Chinese medicine (TCM) is commonly used in breast cancer therapy, and its use dates back more than 2000 years (Sun 2014). Indeed, 86.4% of patients with breast cancer in China are treated with TCM, such as Chinese medicinal herbs (CMH) (Cui et al. 2004; Chen et al. 2008). It is worth noting that the percentage of Western nations using TCM is growing, with 9–69% of patients in these counties using TCM (Ernst 2000; Harris and Rees 2000). According to study statistics, approximately 65% in Australia and 33.1% in Taiwan of patients with cancer use one form or another of complementary and alternative therapies (CAT), with up to 36% of CAT users opting for TCM (Cooke et al. 2012; Porter et al. 2017). Survivors of

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breast cancer constitute the largest user population. CMH is the most common TCM treatment (Molassiotis et al. 2005; Boon et al. 2007; Cooke et al. 2012; Porter et al. 2017; Kuo et al. 2018). In addition, 25–47% of patients with cancer in North America use herbal remedies to support their therapy (Yin et al. 2013). TCM usage, particularly CMH, is believed to reduce the toxic side effects of cancer treatment, such as relieving hot flashes and bone loss induced by endocrine therapy (Li et al. 2016; Huang et al. 2017), improving immune function (Wong et al. 2005), increasing general well-being and quality of life (Porter et al. 2017), reducing metastasis and recurrence, and prolonging life expectancy (Jiang et al. 2021).

CMH has been suggested as a potentially useful treatment for patients with breast cancer undergoing endocrine therapy. Consequently, the current study sought to perform a meta-analysis and comprehensive systematic review to assess the efficacy of CMH as an adjunctive therapy to minimize the negative impacts of endocrine therapy in breast cancer treatment.

Methods

Design

Detailed findings were presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The PROSPERO registration number for this systematic review is CRD42021262536.

Search strategy

The main electronic databases, including PubMed, Embase, Cochrane Library, Web of Science, clinicaltrials.gov, Ovid, EBSCO, China National Knowledge Information Database (CNKI), Wang Fang, and Chinese Science and Technology Database (CSTJ), were searched using the following search keywords: (Chinese herb OR Chinese herbal medicine OR herb medicine OR Chinese herb therapy OR herbal remedy OR herb therapy) AND (breast neoplasms OR breast cancer OR breast lesions) AND (endocrine therapy) AND (clinical trial OR randomized controlled trial OR randomized controlled trial), with minor modifications based on the specifics of each database search. Only original research publications with a publication date before 20 May 2022 were sourced, and only articles in English and Chinese were considered.

PICOS

Types of studies

Randomized clinical trials (RCTs) were included if they were of patients with breast cancer receiving endocrine therapy.

Participants

All participants were females with HR+ (progesterone receptor and/or estrogen receptor-positive) breast cancer, regardless of cancer stage, age, or race. Patients who did not receive Chinese herbal treatment were excluded from the study.

Interventions and control

CMH (single or compound) was used as the intervention. There were no limitations to the dosage form, dosage, or course of treatment. CMH can be administered before, during, or after endocrine therapy, whether injected or administered orally. This review included studies on CMH versus placebo, CMH in combination with Western drugs versus Western drugs only, or CMH alone versus Western drugs to reduce the side effects of endocrine therapy.

Outcomes

Outcome data were classified as (1) cancer treatment-induced bone loss, including bone mineral density (BMD), beta cross-laps (β-CTX), bone gal protein (BGP), and bone-specific alkaline phosphatase (BALP). (2) Menopausal symptoms, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), Kupperman score, estradiol (E2), and endometrial thickening. (3) Dyslipidemia, including total high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), and cholesterol (TC) levels.

Exclusion criteria

Studies were excluded if they did not include a mean value or standard deviation (SD), if the full text was unavailable, or if neither could be obtained despite repeated attempts to contact the authors. In addition, studies with inadequate methodological quality (Jadad score <3) were excluded.

Study selection

Two reviewers separately examined the titles and abstracts of all studies. Based on the specified inclusion criteria, the entire text matching the inclusion criteria (according to the screening of titles and abstracts) was collected, followed by the retrieval of possibly related references. A consensus was established, or a third investigator was consulted as necessary.

Data extraction

The following data were extracted: general information (publication year, first author's name, and title of study), participant characteristics (sex, age, disease stage, and sample size), intervention characteristics (description of the intervention and control groups, dosage of Western medicine and CMH, treatment duration and frequency), outcome measures (mean, SD, significance level, and units of measurement), and Jadad scale.

Methodological quality assessment

The risk of bias for the included studies was assessed based on the Cochrane Handbook for Systematic Reviews evaluation criteria in the following six domains: performance bias (blinding of personnel and participants), selection bias (concealment of the random sequence generation and allocation), attrition bias (incomplete outcome data), detection bias (blinding of outcome evaluation), reporting bias (reporting selectively), and other biases. Each type of bias was categorized as high, low, or unclear. For the generation of random sequencing, low risk means that the researcher has specified how the random sequence was generated, such as random numbers generated by a computer or randomized digital table. In contrast, there is a high risk if random sequence generation contains no random component. For allocation concealment, a low risk refers to the inability of the subject or investigator to predict the assignment, such as using a central randomization system or an ordered, opaque envelope.

For performance bias, low risk conditions were considered if the outcome was not affected by a lack of blinding of participants. Likewise, there is a minimal risk of detection bias when the evaluators are blinded or blinding is not implemented but does not affect the results. Low risk conditions were judged when no missing data or missing data did not affect the outcome or the correct way to count the lost data. Selective bias: low risk means that there is an available study protocol, or there is no study protocol, and all expected outcomes have been reported, whereas a high risk means that significant results are not reported or incomplete. Two authors independently determined whether each area had low, high, or unclear bias. When there was disagreement between the two reviewers, a third reviewer was consulted to help reach a decision.

Statistical analyses

The Cochrane Collaboration Review Manager Software (RevMan 5.3.0) was used for the data analysis. For all included studies, all outcome data were presented as the mean ± SD, and the rate of adverse reactions was reported as dichotomous data. To evaluate the heterogeneity, I^2 values were determined. If I^2 was ≤25%, we used a fixed-effects model; otherwise, if I^2 was > 25%, we adopted a random-effects model. In this study, breast cancer subgroups were determined based on TCM syndrome differentiation principles, which primarily involve two factors: strengthening the body (+), Bu Shen, or a combination of strengthening and removing pathological products (±), Bu Shen shu gan. Funnel plots were used to assess the possibility of publication bias.

Results

Characteristics of included studies

Database searches identified 923 studies, of which 628 records remained after removing duplicates. Furthermore, 561 articles were excluded after their titles and abstracts were reviewed because they involved animal experiments, combined other complications, were narrative reviews or protocols and were not clinical studies related to CMH and endocrine therapy. After reading the full texts of 67 papers, 13 studies with no relevant outcomes, one study that compared different CMH, five duplicate studies, and 17 trials with a Jadad score (less than three points) indicating poor methodological quality were excluded. Therefore, 31 studies (Zhang and Zheng 2012; Bian et al. 2013; Wang et al. 2013; Shi et al. 2014; Sun et al. 2014; Fu et al. 2015; Xia and Wang 2015; Guo et al. 2016; Wu et al. 2016; Yang et al. 2016; Li and Liang 2017; Shi et al. 2017; Wang et al. 2017; Zhu 2017; Cai et al. 2018; Hu 2018; Gong 2019; Gong et al. 2019; Li et al. 2019; Pei and Sun 2019; Xiao et al. 2019; Guo et al. 2020; Hu et al. 2020; Qiu et al. 2020; Tao et al. 2020; Zhang et al. 2020; Zhong et al. 2020; Zhou et al. 2020; Cai et al. 2021; Li and Li 2021; Liu et al. 2021) were included in the meta-analysis. Figure 1 shows a flowchart of the article search procedure.

The included studies involved 2288 patients, including 1117 patients in the control group and 1130 patients in the CMH group, with 41 patient dropouts. All included patients were pathologically diagnosed with HR(+) breast cancer. Table 1 displays the baseline characteristics of the included studies. And Table 2 displays Chinese herbal components of the included studies.

Risk of bias within studies

As shown in Figure 2, all 31 studies reported randomization; however, one study did not report the randomization method (Wang et al. 2013). Two studies (Cai et al. 2018; Gong et al. 2019) reported allocation concealment, two studies (Cai et al. 2018; Gong et al. 2019) reported double-blinding, and one (Zhou et al. 2020) reported blinding using placebos as controls. The performance bias of these three studies was assessed as low risk. The detection bias of eight studies (Wang et al. 2013; Li and Liang 2017; Shi et al. 2017; Zhu 2017; Cai et al. 2018; Gong et al. 2019; Hu et al. 2020; Zhou et al. 2020) was assessed as low risk for using objective measures, while the remaining 23 studies were judged as unclear. Regarding reporting bias, one study (Qiu et al. 2020) reported negative and positive results and was judged low risk, while the rest were considered unclear. The attrition bias of all studies was unclear.

Endocrine therapy-induced bone loss

Bone mineral density (BMD)

Five RCTs (Xia and Wang 2015; Li and Liang 2017; Shi et al. 2017; Zhu 2017; Zhong et al. 2020) analyzed the BMD level (five included the lumbar BMD, and three included the femoral neck BMD) and showed a significant pooled mean improvement in the BMD of the lumbar spine (Figure 3(A), MD:0.08, 95% CI:0.07–0.09, $p < 0.00001$, $I^2 = 0\%$) and femoral neck (Figure 3(B), MD:0.08, 95% CI:0.07–0.10, $p < 0.00001$, $I^2 = 7\%$).

Bone-specific alkaline phosphatase (BALP)

Four RCTs (Li and Liang 2017; Shi et al. 2017; Zhu 2017; Guo et al. 2020) including 262 patients (134 in CMH groups and 128 in control groups) showed that CMH decreased the BALP level (MD: −10.31, 95% CI: −21.72 to 1.11, $p = 0.08$, $I^2 = 99\%$) compared to the control group (Figure 3(C)). The sensitivity analysis showed that the heterogeneity remained high even after removing the studies one by one.

Beta cross-laps (B-CTX)

In two studies (Zhu 2017; Guo et al. 2020) that compared CMH to a control group, the amount of B-CTX was significantly reduced by CMH (Figure 3(D), $MD = -0.17$; 95% CI: −0.20 to −0.15, $p<0.00001$, $I^2 = 0\%$).

Bone gal protein (BGP)

Three studies (Li and Liang 2017; Zhu 2017; Guo et al. 2020) involving 222 subjects suggested that CMH resulted in significant improvements in BGP compared to the control group (Figure 3(E), MD = 0.24; 95% CI: 0.17–0.31, $p < 0.00001$, $I^2 = 0\%$).

Menopausal symptoms

Estradiol (E2)

The level of E2 was also assessed in 12 studies (Shi et al. 2014; Fu et al. 2015; Wu et al. 2016; Yang et al. 2016; Wang et al. 2017; Hu 2018; Li et al. 2019; Pei and Sun 2019; Xiao et al. 2019; Zhou et al. 2020; Cai et al. 2021; Liu et al. 2021) but CMH had no significant effect ($MD = 0.90$; 95% CI: −0.31 to 2.12, $p = 0.15$, $I^2 = 73\%$). Subgroup analysis also showed no significant effect in either the Bu Shen or Bu Shen shu gan subgroups (Figure 4(A), $MD = 1.59$; 95% CI: −0.15 to 3.32, $p = 0.07$, $I^2 = 47\%$, and

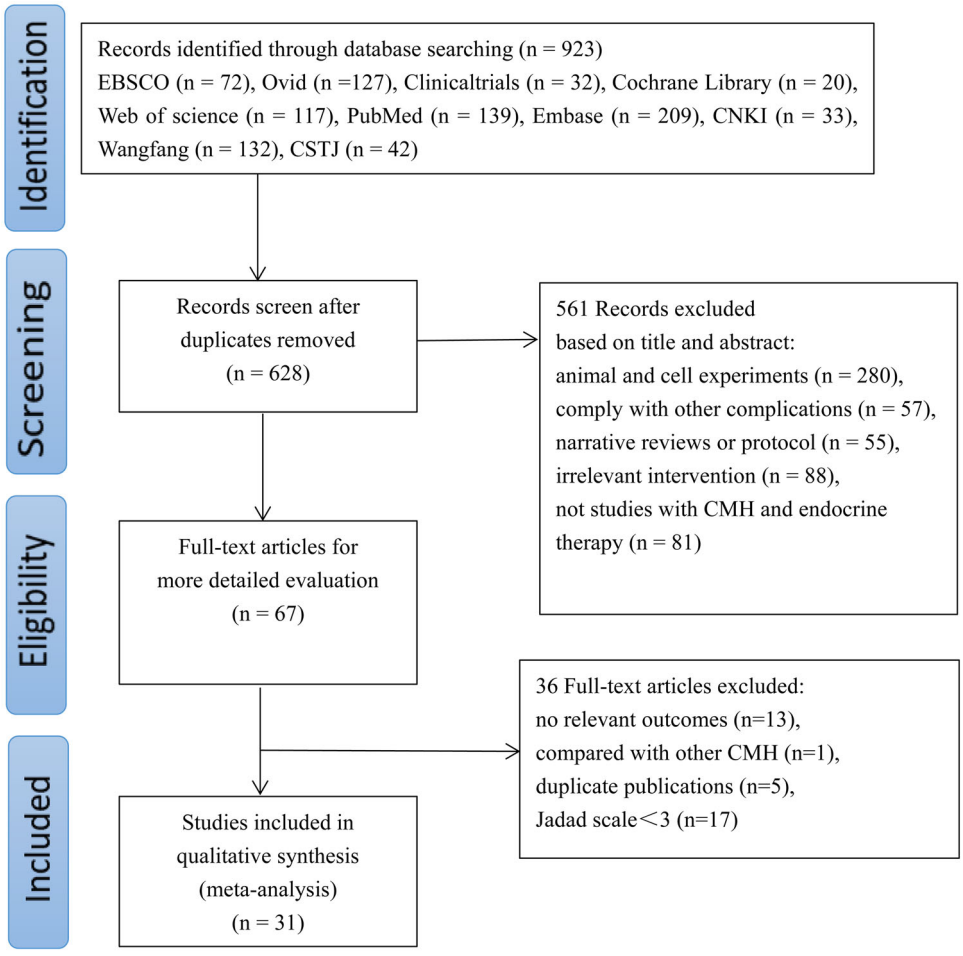

Figure 1. Flowchart of the article-searching procedure. CSTJ: Chinese Science and Technology Database; CNKI: China National Knowledge Information database, CMH: Chinese medicinal herbs.

$MD = 0.03$; 95% CI: −0.28 to 0.34, $p = 0.87$, $I^2 = 0\%$, respectively).

Follicle-stimulating hormone (FSH)

Regarding the FSH level, the reduction of FSH in the CMH group was not significantly different from the control group ($MD = -1.55$; 95% CI: −3.33 to 0.23, $p = 0.09$, $I^2 = 77\%$) in 12 studies (Shi et al. 2014; Fu et al. 2015; Wu et al. 2016; Yang et al. 2016; Wang et al. 2017; Hu 2018; Li et al. 2019; Pei and Sun 2019; Xiao et al. 2019; Zhou et al. 2020; Cai et al. 2021; Liu et al. 2021) that included 861 patients (Figure 4(B)). Subgroup analysis of Bu Shen shu gan also showed no significant difference ($MD = -0.07$; 95% CI: −1.12 to 0.98, $p = 0.90$, $I^2 = 0\%$), whereas subgroup analysis of Bu Shen showed a significant decrease in FSH (Figure 4(B), $MD = -4.55$; 95% CI: −8.52 to −0.58, $p = 0.02$, $I^2 = 86\%$).

Luteinizing hormone (LH)

For the LH level, ten studies (Shi et al. 2014; Fu et al. 2015; Wu et al. 2016; Yang et al. 2016; Hu 2018; Li et al. 2019; Pei and Sun 2019; Xiao et al. 2019; Zhou et al. 2020; Cai et al. 2021) involving 735 patients showed no statistically significant difference between the CMH and control groups ($MD = -1.35$; 95% CI: −2.77 to 0.06, $p = 0.06$, $I^2 = 89\%$), whereas subgroup analysis of Bu Shen revealed a significant reduction with Bu Shen CMH ($MD = -4.23$; 95% CI: −7.83, −0.64, $p = 0.02$, $I^2 = 78\%$) (Figure 4(C)). Because all subgroups showed high heterogeneity, other factors influenced the heterogeneity.

Endometrial thickening

Three RCTs (Wang et al. 2013; Shi et al. 2014; Hu 2018) analyzed endometrial thickening in 180 participants, showing that CMH treatment significantly reduced endometrial thickening ($MD = -2.23$, 95% CI: −4.60 to 0.14, $p = 0.07$) with substantive heterogeneity ($I^2 = 94\%$) (Figure 5(A)). The pooled outcome showed low heterogeneity ($I^2 = 0\%$, $p < 0.00001$) with an MD of −3.37 (95% CI −4.22 to −2.51) following sensitivity analysis in which the study of Shi et al. (2014) was excluded.

Kupperman score

Figure 5(B) shows that the CMH-treated group had significantly lower Kupperman scores than the control group (SMD = −1.75; 95% CI: −2.45 to −1.04, $p<0.00001$, $I^2 = 96\%$) in 16 studies of 1170 patients. All studies adopted the amended Kupperman to calculate the Kupperman score, with 13 studies (Zhang and Zheng 2012; Bian et al. 2013; Shi et al. 2014; Sun et al. 2014; Guo et al. 2016; Yang et al. 2016; Wang et al. 2017; Cai et al. 2018; Gong 2019; Gong et al. 2019; Pei and Sun 2019; Xiao et al. 2019; Li and Li 2021) defining the amended Kupperman according to the same criteria (symptom severity multiplied by symptom index, 0–63 points), while the other three (Wu et al. 2016; Tao et al. 2020; Cai et al. 2021) did not specify the grading

Table 1. Characteristics of the included studies.

Author, year	Sample size (EG + CG)/drop-outs	Diseasestage	Endocrine therapy	EG(CMH)	CG	Duration	Outcome	Jadad scale
Bian et al. (2013)	80(40 + 40)/0	Not mentioned	Tamoxifen	Shugan Tiaoyinyang decoction, (±)	No treament	2 months	KPS, TC, TG, LDL and HDL	3
Cai et al. (2018)	50(25 + 23)/2	I–IV	Not shown	Chaiguilongmu Keli, (±)	Placebo	4 weeks	KPS	5
Cai et al. (2021)	60(30 + 30)/0	Not mentioned	Anastrozole	Fuzheng Xiaoliu decoction, (+)	Gamma-oryzanol and Vitamin B6	2 months	KPS, FSH, LH and E2	3
Fu et al. (2015)	60(30 + 30)/0	Not mentioned	Tamoxifen	Heixiaoyao San combined with Shensiwei decoction, (±)	Vitamin B1 and Vitamin B6	2 months	FSH, LH and E2	3
Gong et al. (2019)	84(42 + 42)/0	I–IV	Not shown	Guipi decoction, (+)	Gamma-oryzanol	8 weeks	KPS	3
Gong et al. (2019)	96(48 + 48)/0	Not mentioned	Tamoxifen and goseraline	Shugan Liangxue decoction , (±)	Placebo	28d	KPS	5
Guo et al. (2016)	100(46 + 44)/10	Metastasis or IV	Tamoxifen or Exemestane	Xiangbei Yangrong decoction, (+)	No treament	Until the disease is better	KPS	3
Guo et al. (2020)	60(30 + 30)/0	Not mentioned	SERMs or AIs	Guilu Sanhuang decoction, (+)	CCVD3	6 months	β-CTX and BGP	3
Hu (2018)	75(38 + 37)/0	II–III	Anastrozole	Ruqing decoction, (+)	Gamma-oryzanol	6 weeks	FSH, LH and E2	3
Hu et al. (2020)	60(30 + 30)/0	I–II	Tamoxifen	Chaishao Jieyu Yin, (±)	No treament	6 months	Endometrial thickening	3
Li et al. (2019)	100(50 + 50)/0	Not mentioned	Tamoxifen or Letrozole or Anastrozole or Exemestane	Rehmanniae decoction, (+)	Not placebo	2 months	TC, TG, FSH, LH and E2	3
Li and Li (2021)	60(30 + 30)/0	I–III	Tamoxifen	Chaihu plus modified Longgu Muli decoction, (±)	Gamma-oryzanol	3 months	KPS	3
Li and Liang. (2017)	70(35 + 35)/0	I–III	Letrozole	Bushen therapy, (+)	CCVD3	12 months	BMD, BGP and BALP	3
Liu et al. (2021)	80(33 + 33)/14	II–III	Goserelin and Letrozole	Jiawei Er-xian decoction, (+)	No treament	3 months	LC, LDL, E2 and FSH	3
Pei and Sun (2019)	60(30 + 30)/0	I–IV	Tamoxifen or Toremifene or Letrozole 0r Anastrozole	Danzhi Xiaoyao San Combined with Er-xian decoction, (±)	Gamma-oryzanol and Vitamin B6	4 weeks	KPS, FSH, LH and E2	3
Qiu et al. (2020)	81(41 + 40)/0	I–III	Letrozole	Baohe Pill, (±)	Simvastatin Tablets	4 Weeks	TG, TC, LDL and HDL	3
Shi et al. (2017)	40(23 + 17)/0	Not mentioned	Anastrozole or Letrozole or Exemestane	Longniu Bugu decoction, (+)	CCVD3	6 months	BMD and BALP	4
Shi et al. (2014)	60(30 + 30)/0	Not mentioned	Tamoxifen	Yiyuan Shengjing decoction, (±)	Gamma-oryzanol	4 weeks	KPS, FSH, LH, E2 and Endometial thickness	3
Sun et al. (2014)	100(50 + 50)/0	Not mentioned	Tamoxifen	Fuzheng Xiaoai decoction, (+)	No treament	2 months	KPS	3
Tao et al. (2020)	60(30 + 30)/0	I–IV	Tamoxifen or Letrozole or Anastrozole	Yishen Kang'ai decoction, (+)	Gamma-oryzanol	2 months	KPS	3
Wang et al. (2013)	60(30 + 30)/0	I–III	Tamoxifen	Tiaohe decoction, (±)	No treament	6 months	Endometrial thickening	3
Wang et al. (2017)	60(30 + 30)/0	I–III	Tamoxifen	Yishen chenqian fang, (±)	No treament	3 months	KPS, FSH, LH and E2	3
Wu et al. (2016)	72(30 + 30)/12	Not mentioned	Tamoxifen or Letrozole or Anastrozole	Ruqing decoction, (+)	Gamma-oryzanol	2 weeks	FSH, LH and E2	3
Xia and Wang (2015)	70(35 + 35)/0	Not mentioned	Anastrozole	Jintiange capsules, (+)	CCVD3	16 months	BMD	3
Xiao et al. (2019)	53(25 + 25)/3	I–II	Letrozole	Modified Zhibai Dihuang decoction, (±)	Gamma-oryzanol	8 weeks	KPS, FSH, LH and E2	3
Yang et al. (2016)	138(69 + 69)/0	I–III	Tamoxifen	Er-zhi Pills and Guizhi decoction, (±)	Gamma-oryzanol	8 weeks	KPS, FSH, LH and E2	3
Zhang and zheng (2012)	64(32 + 32)/0	Not mentioned	Tamoxifen	Dan Zhi Xiao Yao San and Er-zhi Pills, (±)	No treament	8 weeks	KPS	3
Zhang et al. (2020)	90(45 + 45)/0	I–II	Tamoxifen or AIs	Sanhuang decoction, (±)	No treament	6 months	TC, TG, LDL and HDL	3
Zhong et al. (2020)	81(41 + 40)/0	I–III	AIs	Spleen-tonifying and Kidney-nourishing Prescription, (+)	CCVD3	6 months	BMD	3
Zhou et al. (2020)	72(36 + 36)/0	Not mentioned	Tamoxifen or Toremifene or Anastrozole or Letrozole or Exemestane	Xiaoyao Ankun decoction, (±)	Placebo	60d	KPS, FSH, LH and E2	3
Zhu (2017)	92(46 + 46)/0	II–IV	Not shown	Xianlinggubao capsules, (+)	CCVD3	24 Weeks	BMD and BGP	3

EG: experimental group; CG: control group; CMH: Chinese medicine herbal; KPS: Kupperman score; TC: total cholesterol; TG: triglycerides; LDL: low density lipoprotein; HDL: high density lipoprotein; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; β-CTX: beta cross-laps; BGP: bone gal protein; BMD: bone mineral density; BALP: bone-specific alkaline phosphatase; CCVD3: Calcium Carbonate and Vitamin D3 Tablets; SERMs: Selective estrogen receptor modulators; AIs: Aromatase inhibitors; ±: Bu Shen shu gan; +: Bu Shen.

Table 2. Chinese herbal components of the included studies.

References	CMH	Components
Bian et al. (2013)	Shugan Tiaoyinyang decoction, (±)	*Curculigo orchioides* Gaertn. 10 g, *Epimedium brevicomu* Maxim. 10 g, *Phellodendron chinense* Schneid. 10 g, *Anemarrhena asphodeloides* Bge. 10 g, *Bupleurum chinense* DC. 10 g, *Curcuma wenyujin* Y. H. Chen et C. Ling 10 g, *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou 10 g.
Cai et al. (2018)	Chaiguilongmu Keli, (±)	*Bupleurum chinense* DC. 10 g, *Cinnamomum cassia* Presl 10 g, *Pinellia ternata*(Thunb.)Breit. 10 g, *Scutellaria baicalensis* Georgi 10 g, *Magnolia officinalis* Rehd. et Wils. 10 g, *Paeonia lactiflora* Pall.20 g, Os Draconis 30 g, *Ostrea gigas* Thunberg 30 g, *Curcuma wenyujin* Y. H. Chen et C. Ling 15 g, *Lycopodium japonicum* Thunb. 15 g, *Cyathula officinalis* Kuan 15 g, *Glycyrrhiza uralensis* Fisch. 6 g.
Cai et al. (2021)	Fuzheng Xiaoliu decoction, (+)	*Coix lacryma-jobi* L.var.*mayuen*(Roman.) Stapf 30 g, *Agrimonia pilosa* Ledeb. 30 g, *Oldenlandia diffusa* (Willd.) Roxb. 30 g, *Panax quinquefolium* L. 15 g, *Ganoderma lucidum* (Leyss.ex Fr.) Karst. 15 g, *Sparganium stoloniferum* Buch.-Ham. 15 g, *Curcuma phaeocaulis* VaL. 15 g, *Cremastra appendiculata* (D.Don) Makino 15 g, *Pinellia ternata* (Thunb.) Breit. 10 g, *Citrus reticulata* Blanco 10 g, *Polyporus umbellatus* (Pers.) Fries 10 g, *Lilium lancifolium* Thunb. 10 g, *Scutellaria barbata* D. Don 10 g, *Glycyrrhiza uralensis* Fish. 10 g, *Dioscorea bulbifera* L. 5 g.
Fu et al. (2015)	Heixiaoyao San combined with Shensiwei decoction, (±)	*Bupleurum chinense* DC. 15 g, *Paeonia lactiflora* Pall. 15 g, *Angelica sinensis* (Oliv.) Diels 12 g, *Atractylodes macrocephala* Koidz. 12 g, *Poria cocos* (Schw.) Wolf 20 g, *Glycyrrhiza uralensis* Fish.10 g, *Rehmannia glutinosa* Libosch. 12 g, *Lycium barbarum* L. 12 g, *Cuscuta australis* R.Br. 12 g, *Epimedium brevicomu* Maxim. 12 g, *Psoralea corylifolia* L. 12 g, *Polygonum multiflorum* Thunb. 12 g. If fever was identified, *Paeonia suffruticosa* Andr. 10 g, *Gardenia jasminoides* Ellis 10 g were added.
Gong. (2019)	Guipi decoction, (+)	*Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.)Hsiao 15 g, *Codonopsis pilosula* (Franch.) Nannf. 15 g, *Atractylodes macrocephala* Koidz. 10 g, *Glycyrrhiza uralensis* Fisch. 12g, *Zingiber officinale* Rosc. 10 g,*Ziziphus jujuba* Mill. 10 g, *Angelica sinensis* (Oliv.) Diels 10 g, *Poria cocos* (Schw.) Wolf 10 g, *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou 15 g, *Dimocarpus longan* Lour. 10 g, *Polygala tenuifolia* Willd. 10 g, *Aucklandia lappa* Decne. 10 g, *Ligustrum lucidum* Ait. 10 g, *Eclipta prostrata* L. 10 g.
Gong et al. (2019)	Shugan Liangxue decoction, (±)	*Bupleurum chinense* DC. 10 g, *Curcuma wenyujin* Y. H. Chen et C. Ling 20 g, *Arnebia euchroma* (Royle) Johnst. 6 g, *Paeonia lactiflora* Pall. 10 g, *Paeonia suffruticosa* Andr. 10 g, *Cynanchum atratum* Bge. 10 g, *Schisandra chinensis* (Turcz.) Baill. 10 g.
Guo et al. (2016)	Xiangbei Yangrong decoction, (+)	*Panax ginseng* C. A. Mey. 10 g, *Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao 30 g, *Poria cocos* (Schw.) Wolf 20 g, *Rehmannia glutinosa* Libosch. 30 g, *Ligusticum chuanxiong* Hort. 15 g, *Angelica sinensis* (Oliv.) Diels 10 g, *Fritillaria thunbergii* Miq. 15 g, *Cyperus rotundus L.* 10 g, *Ranunculus ternatus* Thunb. 20 g, *Euonymus alatus* (Thunb.) Sieb. 20 g, *Prunella vulgaris* L. 15 g, *Sparganium stoloniferum* Buch.-Ham. 10 g, *Curcuma phaeocaulis* VaL. 10 g, *Glycyrrhiza uralensis* Fish. 6 g.
Guo et al. (2020)	Guilu Sanhuang decoction, (+)	*Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao 30 g, *Curcuma Longa* L. 10 g, *Rheum palmatum* L. 10 g, *Cervus elaphus* Linnaeus(melting*) 6 g, *Chinemys reevesii* (Gray) (melting*) 6 g.
Hu (2018)	Ruqing decoction, (+)	*Ostrea gigas* Thunberg(calcining*) 20 g, *Dioscorea opposita* Thunb. 15 g, *Pseudostellaria heterophylla* (Miq.) Pax ex Pax et Hoffm. 12 g, *Ophiopogon japonicus* (L.f.) Ker-Gawl. 12 g, *Rehmannia glutinosa* Libosch. 10 g, *Scrophularia ningpoensis* Hemsl. 10 g, *Poria cocos* (Schw.) Wolf 10 g, *Schisandra chinensis* (Turcz.) Baill. 10 g, *Paeonia suffruticosa* Andr. 8 g, *Chinemys reevesii* (Gray) 8 g, *Sagittaria trifolia* Linn. var.*sinensis*(Sims) Makino 6 g, *Glycyrrhiza uralensis* Fish. 6 g, *Buthus martensii* Karsch 5 g.
Hu et al. (2020)	Chaishao Jieyu Yin, (±)	*Bupleurum chinense* DC. 15 g, *Paeonia lactiflora* Pall. 25 g, *Citrus aurantium* L.(stir-frying*) 15 g, *Curcuma wenyujin* Y. H. Chen et C. Ling 20 g, *Oldenlandia diffusa* (Willd.) Roxb. 20 g, *Akebia quinata* (Thunb.)Decne 20 g, *Acorus tatarinowii* Schott 20 g, *Lilium lancifolium* Thunb. 20 g, *Polygala tenuifolia* Willd. 20 g, *Angelica sinensis* (Oliv.) Diels 20 g, *Scrophularia ningpoensis* Hemsl. 20 g, *Prunella vulgaris* L. 20 g, *Tribulus terrestris* L. 20 g, *Paeonia suffruticosa* Andr. 20 g, Os Draconis 25 g, *Psoralea corylifolia* L. 25 g, *Cuscuta australis* R.Br. 25 g, *Glycyrrhiza uralensis* Fish. 25 g, *Hordeum vulgare* L. 30 g.
Li et al. (2019)	Rehmanniae decoction, (+)	*Rehmannia glutinosa* Libosch. 15 g, *Morinda officinalis* How 12 g, *Cornus officinalis* Sieb. et Zucc. 9 g, *Dendrobium nobile* Lindl. 6 g, *Cistanche deserticola* Y.C.Ma 12 g, *Aconitum carmichaelii* Debx. 6 g, *Schisandra chinensis* (Turcz.) Baill. 6 g, *Cinnamomum cassia* Presl 3 g, *Poria cocos* (Schw.) Wolf 15 g, *Ophiopogon japonicus* (L.f.) Ker-Gawl. 15 g, *Acorus calamus* L. 6 g, *Polygala tenuifolia* Willd. 9 g.
Li and Li (2021)	Chaihu plus modified Longgu Muli decoction, (±)	*Bupleurum chinense* DC. 15 g, *Cinnamomum cassia* Presl 9 g, *Poria cocos* (Schw.) Wolf 12 g, *Pinellia ternata*(Thunb.)Breit. 9 g, *Scutellaria baicalensis* Georgi 9 g, *Ostrea gigas* Thunberg 30 g, *Codonopsis pilosula* (Franch.)Nannf. 12 g, *Rheum palmatum* L. 6 g, Os Draconis 30 g, *Psoralea corylifolia* L. 12 g, *Lycium barbarum* L. 12 g, *Cuscuta australis* R.Br. 12 g, *Epimedium brevicomu* Maxim. 12 g, *Ziziphus jujuba* Mill. 20 g, *Zingiber officinale* Rosc. 9 g.

(*continued*)

Table 2. Continued.

References	CMH	Components
Li and Liang (2017)	Bushen therapy, (+)	*Dioscorea opposita* Thunb. 15 g, *Poria cocos* (Schw.) Wolf 15 g, *Psoralea corylifolia* L. 15 g, *Taxillus chinensis* (DC.) Danser 30 g, *Drynaria fortunei* (Kunze) J.Sm. 15 g, *Achyranthes bidentata* Bl. 15 g, *Spatholobus suberedus* Dunn 30 g, *Ficus simplicissima* Lour. 20 g, *Cibotium barometz* (L.) J.Sm. 15 g, *Atractylodes macrocephala* Koidz. 15 g.
Liu et al. (2021)	Jiawei Er-xian decoction, (+)	*Curculigo orchioides* Gaertn. 15 g, *Epimedium brevicomu* Maxim. 15 g, *Morinda officinalis* How 9 g, *Phellodendron chinense* Schneid. 9 g, *Anemarrhena asphodeloides* Bge. 9 g, *Angelica sinensis* (Oliv.) Diels 9 g,*Triticum aestivum* L. 15 g, *Ostrea gigas* Thunberg(calcining*) 15 g, Astragali Radix 15 g, If sweating was identified Os Draconis 20 g, *Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao 15 g, and *Ephedra sinica* Stapf 5 g were added.
Pei and Sun (2019)	Danzhi Xiaoyao San Combined with Er-xian decoction, (±)	*Paeonia suffruticosa* Andr. 9 g, *Gardenia jasminoides* Ellis 15 g, *Bupleurum chinense* DC. 10 g, *Angelica sinensis* (Oliv.) Diels 15 g, *Paeonia veitchii* Lynch 15 g, *Atractylodes macrocephala* Koidz. 30 g, *Poria cocos* (Schw.) Wolf 30 g, *Curculigo orchioides* Gaertn. 15 g, *Epimedium brevicomu* Maxim. 15 g, *Anemarrhena asphodeloides* Bge. 15 g, *Phellodendron chinense* Schneid. 15 g, *Morinda officinalis* How 15 g, *Mentha haplocalyx* Briq. 10 g, *Glycyrrhiza uralensis* Fish.(stir-frying with honey*) 6 g.
Qiu et al. (2020)	Baohe Pill, (±)	*Crataegus pinnatifida* Bge. var. major N. E. Br.(stir-frying*) 15g, Massa Medicata Fermentata 20g, *Pinellia ternata*(Thunb.)Breit. 15 g, *Poria cocos* (Schw.) Wolf 15 g, *Citrμs reticμlata* Blanco 15g, *Forsythia suspensa* (Thunb.) Vahl 15g, *Raphanus sativus* L.(stir-frying*) 15 g, *Hordeum vulgare* L.(stir-frying*) 15 g, *Cassia obtusifolia* L. 15 g, *Salvia miltiorrhiza* Bge. 10 g, *Codonopsis pilosula* (Franch.)Nannf. 15 g, *Achyranthes bidentata* Bl. 15 g, *Cyperus rotundus L.* 10 g, *Glycyrrhiza uralensis* Fish.(stir-frying with honey*) 3 g.
Shi et al. (2017)	Longniu Bugu decoction, (+)	*Achyranthes bidentata* Bl. 20 g, *Psoralea corylifolia* L. 20 g, Os Draconis(calcining*) 30 g, *Ostrea gigas* Thunberg(calcining*) 30 g.
Shi et al. (2014)	Yiyuan Shengjing decoction, (±)	*Anemarrhena asphodeloides* Bge. 10 g, *Phellodendron chinense* Schneid. 10 g, *Angelica sinensis* (Oliv.) Diels 8 g, *Curculigo orchioides* Gaertn. 8 g, *Epimedium brevicomu* Maxim. 12 g, *Morinda officinalis* How 12 g, *Rehmannia glutinosa* Libosch. 12 g, *Eucommia ulmoides* Oliv. 12 g, *Eclipta prostrata* L. 12 g, *Cervus elaphus* Linnaeus(melting*) 12 g.
Sun et al. (2014)	Fuzheng Xiaoai decoction, (+)	*Rehmannia glutinosa* Libosch. 30 g, *Ligustrum lucidum* Ait. 15 g, *Morus alba* L. 20 g, *Cuscuta australis* R.Br. 15 g, *Lycium barbarum* L. 30 g, *Epimedium brevicomu* Maxim. 12 g, *Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao 20 g, *Pseudostellaria heterophylla* (Miq.) Pax ex Pax et Hoffm. 30 g, *Dioscorea opposita* Thunb. 15 g, *Poria cocos* (Schw.) Wolf 15 g, *Atractylodes macrocephala* Koidz. 15 g,*Oldenlandia diffusa* (Willd.) Roxb. 30 g, *Scutellaria barbata* D. Don 20 g, *Taraxacum mongolicum* Hand. -Mazz. 15 g, *Ranunculus ternatus* Thunb. 15 g, *Sparganium stoloniferum* Buch.-Ham. 15 g, *Curcuma phaeocaulis* VaL. 15 g.
Tao et al. (2020)	Yishen Kang'ai decoction, (+)	*Ligustrum lucidum* Ait. 12g, *Eclipta prostrata* L. 12 g, *Viscum coloratum* (Komar.) Nakai 15 g, *Dipsacus asper* Wall. Ex Henry 15 g, *Cremastra appendiculata* (D.Don) Makino 12 g, *Ostrea gigas* Thunberg 15 g, *Smilax glabra* Roxb. 15 g, *Trichosanthes kirilowii* Maxim. 20 g, *Polygonatum kingianum* Coll.et Hemsl. 30 g, *Polygonum multiflorum* Thunb. 15 g, *Atractylodes macrocephala* Koidz.(stir-frying*) 15 g, *Poria cocos* (Schw.) Wolf 15 g, *Triticum aestivum* L. 15 g, *Gallus gallus domesticus* Brisson 12 g.
Wang et al. (2013)	Tiaohe decoction, (±)	*Bupleurum chinense* DC. 15 g, *Paeonia lactiflora* Pall. 15 g, *Ligustrum lucidum* Ait. 15 g, *Cuscuta australis* R.Br. 30 g, *Rehmannia glutinosa* Libosch. 20 g, *Dioscorea opposita* Thunb. 10 g, *Laminaria japonica* Aresch. 15 g, *Fritillaria thunbergii* Miq. 10 g, *Anemarrhena asphodeloides* Bge. 15 g, *Poria cocos* (Schw.) Wolf 15 g, *Atractylodes macrocephala* Koidz. 15 g.
Wang et al. (2017)	Yishen chenqian fang, (±)	*Rehmannia glutinosa* Libosch. 10 g, *Anemarrhena asphodeloides* Bge. 10 g, *Curculigo orchioides* Gaertn. 10 g, *Epimedium brevicomu* Maxim. 10 g, *Morinda officinalis* How 10 g, *Angelica sinensis* (Oliv.) Diels 10 g, *Paeonia lactiflora* Pall. 10 g, Os Draconis 10 g, *Phellodendron chinense* Schneid. 10 g, *Poria cocos* (Schw.) Wolf 10 g, *Atractylodes macrocephala* Koidz(stir-frying*) 10 g, *Taxillus chinensis* (DC.) Danser 10 g, *Lycium barbarum* L. 10 g, *Ostrea gigas* Thunberg(calcining*) 30 g, *Amygdalus persica* L.[*Prunus persica* (L.) Batsch.]30 g, *Ephedra sinica* Stapf 15 g, *Cremastra appendiculata* (D.Don) Makino 15 g, *Rha ponticum uniflorum* (L.) DC. 20 g,*Glycyrrhiza uralensis* Fish.(stir-frying with honey*) 6 g.
Wu et al. (2016)	Ruqing decoction, (+)	*Ophiopogon japonicus* (L.f.) Ker-Gawl. 20 g, *Schisandra chinensis* (Turcz.) Baill. 12 g, *Rehmannia glutinosa* Libosch. 20 g, *Scrophularia ningpoensis* Hemsl. 20 g, *Dioscorea opposita* Thunb. 20 g, *Poria cocos* (Schw.) Wolf 20 g, *Paeonia suffruticosa* Andr. 12 g, *Pseudostellaria heterophylla* (Miq.) Pax ex Pax et Hoffm. 20 g, *Coptis chinensis* Franch. 9 g, *Chinemys reevesii* (Gray) (calcining*) 20 g, *Buthus martensii* Karsch 9 g, *Cremastra appendiculata* (D.Don) Makino 10 g, *Cornus officinalis* Sieb. et Zucc. 12 g, *Ostrea gigas* Thunberg(calcining*) 50 g, *Glycyrrhiza uralensis* Fish.(stir-frying with honey*) 6 g.

(*continued*)

Table 2. Continued.

References	CMH	Components
Xia and Wang (2015)	Jintiange capsules, (+)	Artificial tiger-bone power.
Xiao et al. (2019)	Modified Zhibai Dihuang decoction, (±)	*Anemarrhena asphodeloides* Bge. 10 g, *Phellodendron chinense* Schneid. 6 g, *Rehmannia glutinosa* Libosch. 10 g, *Rehmannia glutinosa* Libosch. 10 g, *Dioscorea opposita* Thunb. 10 g, *Cornus officinalis* Sieb. et Zucc. 12 g, *Paeonia suffruticosa* Andr. 10 g, *Poria cocos* (Schw.) Wolf 10 g, *Alisma orientate* (Sam.) Juzep. 10 g, *Ligustrum lucidum* Ait. 10 g, *Epimedium brevicomu* Maxim. 10 g, *Eclipta prostrata* L. 10 g, *Glycyrrhiza uralensis* Fisch. 5 g.
Yang et al. (2016)	Er-zhi Pills and Guizhi decoction, (±)	*Ligustrum lucidum* Ait. 10 g, *Eclipta prostrata* L. 10 g, *Cinnamomum cassia* Presl 9 g, *Paeonia lactiflora* Pall. 9 g, *Zingiber officinale* Rosc. 9 g, *Glycyrrhiza uralensis* Fisch.(stir-frying with honey*) 6 g, *Ziziphus jujuba* Mill 20 g.
Zhang and Zheng (2012)	Dan Zhi Xiao Yao San and Er-zhi Pills, (±)	*Rehmannia glutinosa* Libosch., *Cornus officinalis* Sieb. et Zucc., *Paeonia suffruticosa* Andr., *Gardenia jasminoides* Ellis(stir-frying*), *Bupleurum chinense* DC., *Cyperus rotundus L.*(processing with vinegar*), *Atractylodes macrocephala* Koidz., *Poria cocos* (Schw.) Wolf, *Angelica sinensis* (Oliv.) Diels, *Paeonia lactiflora* Pall., *Citrμs reticμlata* Blanco, *Ligustrum lucidum* Ait., *Eclipta prostrata* L., *Lilium lancifolium* Thunb., *Hordeum vulgare* L.(stir-frying*), *Crataegus pinnatifida* Bge. var. major N. E. Br.(stir-frying*).
Zhang et al. (2020)	Sanhuang decoction, (±)	*Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao(stir-frying with honey*) 30 g, *Curcuma Longa* L.10 g, *Rheum palmatum* L. 10 g,
Zhong et al. (2020)	Spleen-tonifying and Kidney-nourishing Prescription, (+)	*Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao 30 g, *Rehmannia glutinosa* Libosch. 15 g, *Dioscorea opposita* Thunb. 15 g, *Alisma orientate* (Sam.) Juzep. 15 g, *Cornus officinalis* Sieb. et Zucc. 9 g, *Poria cocos* (Schw.) Wolf 12 *g, Paeonia suffruticosa* Andr. 12 g.
Zhou et al. (2020)	Xiaoyao Ankun decoction, (±)	*Bupleurum chinense* DC. 8 g, *Atractylodes macrocephala* Koidz. 30 g, *Poria cocos* (Schw.) Wolf 15 g, *Angelica sinensis* (Oliv.) Diels 15 g, *Paeonia lactiflora* Pall. 15 g, *Mentha haplocalyx* Briq. 10 g, *Ligustrum lucidum* Ait. 15 g, *Eclipta prostrata* L. 15 g, *Rehmannia glutinosa* Libosch. 15 g, *Cornus officinalis* Sieb. et Zucc. 15 g, *Citrus reticulata* Blanco 15 g, *Litchi chinensis* Sonn. 15 g, *Citrus reticulata* Blanco 10 g, *Taraxacum mongolicum* Hand. -Mazz. 15 g, *Oldenlandia diffusa* (Willd.) Roxb. 15 g, Gekko japonicus Dumeril et Bibron 10 g, *Glycyrrhiza uralensis* Fisch. 10 g.
Zhu (2017)	Xianlinggubao capsules, (+)	*Epimedium brevicomu* Maxim., *Dipsacus asper* Wall. Ex Henry, *Codonopsis pilosula* (Franch.)Nannf., *Anemarrhena asphodeloides* Bge., *Psoralea corylifolia* L., *Rehmannia glutinosa* Libosch.

CMH: Chinese medicinal herbs; ±: Bu Shen shu gan; +: Bu Shen; *: the method of preparation.

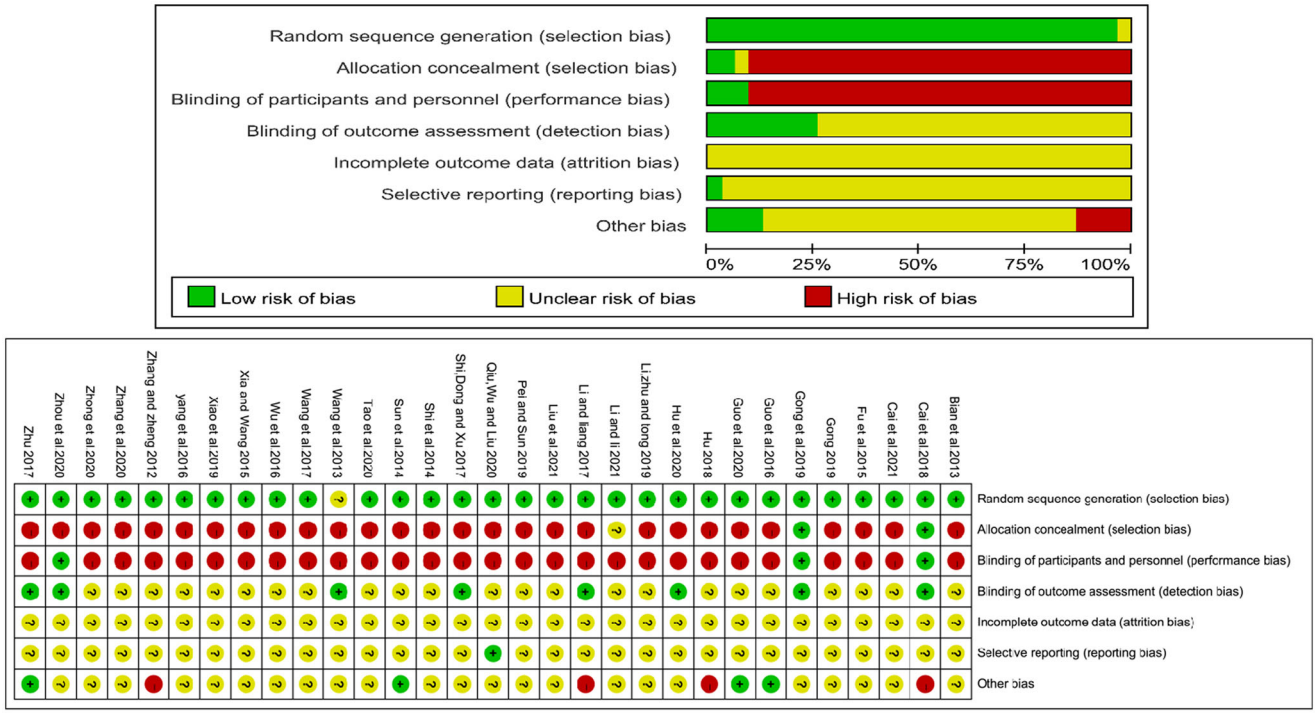

Figure 2. Risk of bias (A: Risk of bias of the included studies, B: Risk of bias of the individual studies. +: low risk of bias; −: high risk of bias;? : unclear risk of bias).

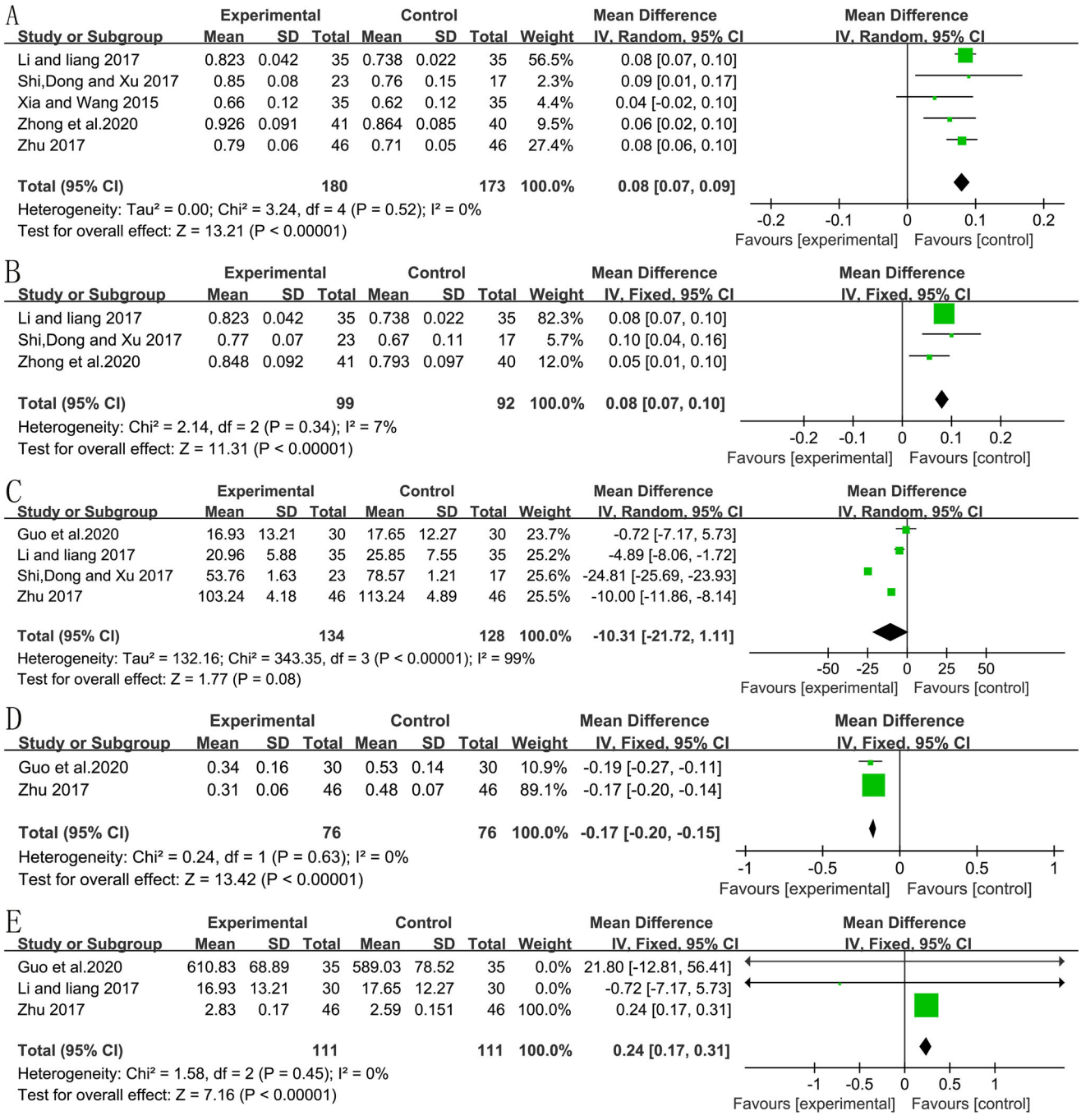

Figure 3. Meta-analysis of CMH on endocrine therapy-induced bone loss of patients with HR + breast cancer (A: lumber BMD, B: neck BMD, C: BALP, D: B-CTX, E: BGP).

methods. However, the meta-analysis showed the same results after removing these articles. The subgroup analysis showed that the Kupperman score was also significantly reduced in each subgroup. Notably, each subgroup also showed high heterogeneity, indicating that other factors affected the heterogeneity.

Dyslipidemia

Total cholesterol (TC). Five RCTs (Bian et al. 2013; Li et al. 2019; Qiu et al. 2020; Zhang et al. 2020; Liu et al. 2021), including 417 participants, showed a significant reduction in TC ($MD = -0.67$, 95% CI: −1.08 to −0.25, $p = 0.002$) in the CMH-treated group compared to the control group. However, the heterogeneity among the studies was $I^2 = 86\%$ and remained unchanged after the sensitivity analysis (Figure 6(A)).

Triglycerides (TG). The pooled results showed that CMH treatment significantly reduced TG compared to the control group ($MD = -0.53$, 95% CI: −1.00 to −0.07, $p < 0.00001$). However, a sensitivity analysis was conducted due to the substantial heterogeneity among the studies ($I^2 = 98\%$) (Figure 6(B)). The heterogeneity was significantly reduced ($I^2 = 0\%$) when the study by Zhang et al. (2020) was removed.

Low-density lipoprotein (LDL). Four RCTs (Bian et al. 2013; Qiu et al. 2020; Zhang et al. 2020; Liu et al. 2021) with 317 participants showed a significant reduction in LDL ($MD = -0.41$, 95%

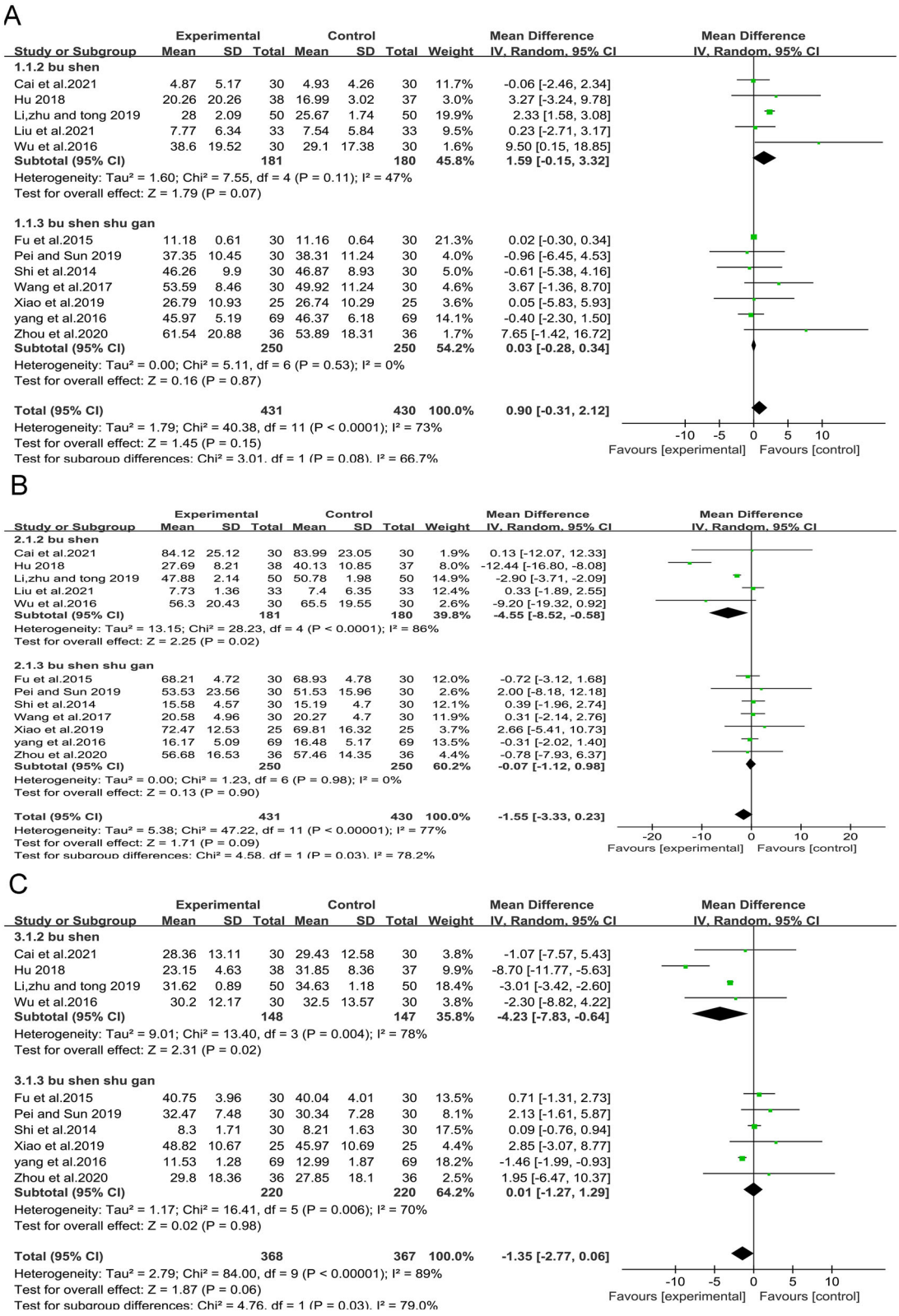

Figure 4. Meta-analysis of CMH on serum gonadal hormone concentration of patients with HR + breast cancer treated with endocrine therapy (A: E2, B: FSH, C: LH).

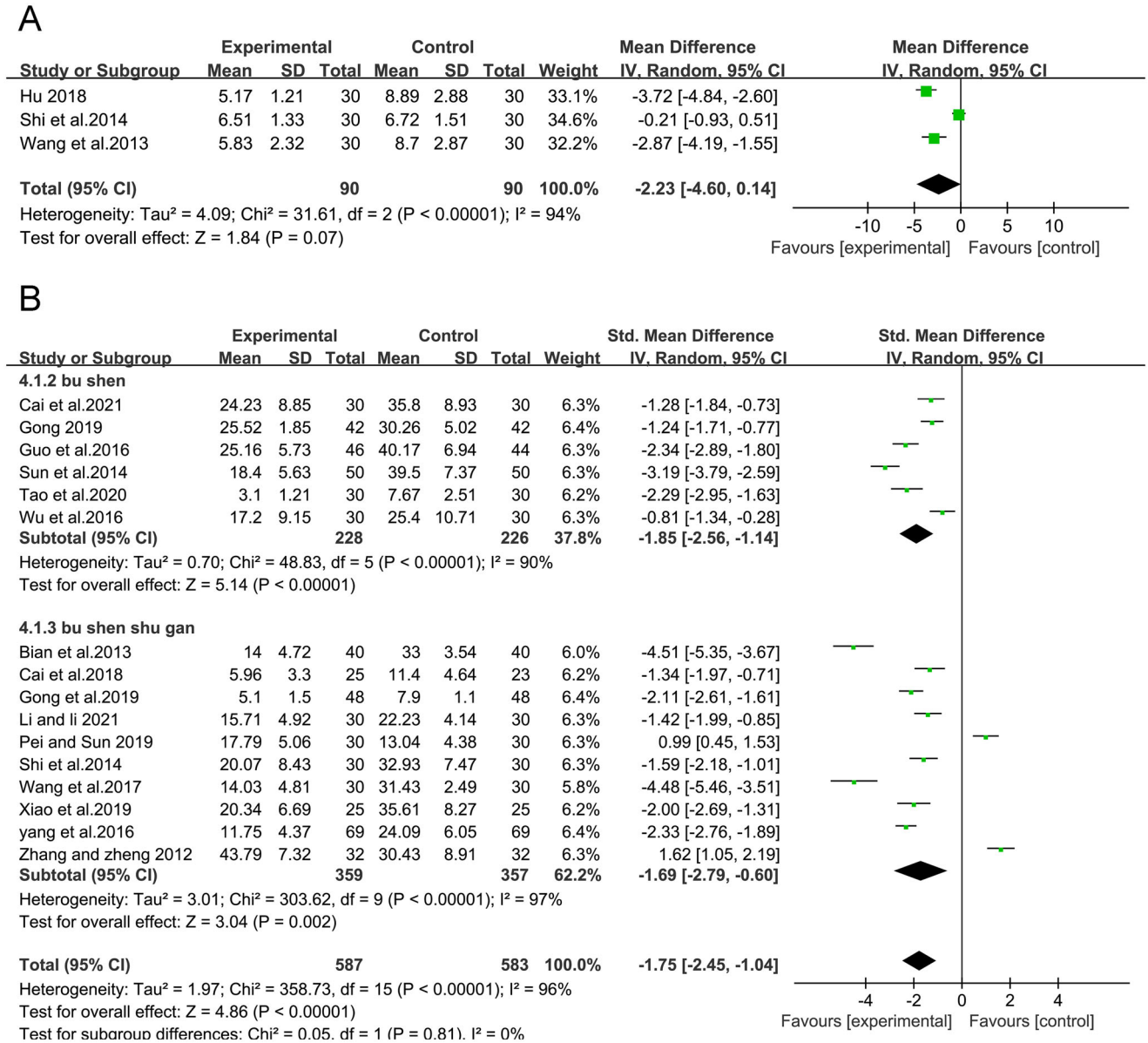

Figure 5. Meta-analysis of CMH on endocrine therapy-induced menopausal symptoms of patients with HR + breast cancer (A: Endometrial thickening, B: Kupperman score).

CI: −0.62 to −0.19, $p = 0.0002$) in the CMH-treated group compared to the control group. Again, the heterogeneity among the studies was $I^2 = 80\%$ and remained unchanged following sensitivity analysis, in which those studies were excluded (Figure 6(C)).

High-density lipoprotein (HDL). The meta-analysis also showed no statistically significant difference between the CMH and control groups in improving HDL levels ($MD = 0.07$, 95% CI: −0.10 to 0.23, $p = 0.43$, $I^2 = 89\%$) (Figure 6(D)).

Publication bias

The asymmetric funnel plots in Figure 7(A–C) indicate a publication bias for E2, FSH, and LH. The funnel plot in Figure 7(D) shows an almost symmetrical distribution, indicating no publication bias in the Kupperman score. For the other outcomes, funnel plot analysis was not conducted because of the insufficient number of studies included.

Discussion

CMH has been used clinically to relieve adverse effects experienced by patients with breast cancer. Multiple systematic reviews and meta-analyses have evaluated the efficacy of CMH in patients with breast cancer to prevent chemotherapy-related adverse effects (Zhang et al. 2007; Kim et al. 2015; Leggett et al. 2015; Zhu et al. 2016; Zhu 2017; Li et al. 2020). However, few studies have assessed the effectiveness of CMH treatment on side effects associated with endocrine therapy in HR(+) breast cancer. This study aimed to perform a comprehensive meta-analysis and systematic review to investigate whether CMH can reduce endocrine therapy-induced adverse effects in patients with HR(+) breast cancer.

This meta-analysis revealed a significant alleviation of bone loss (measured by BMD and BGP) and dyslipidemia (measured

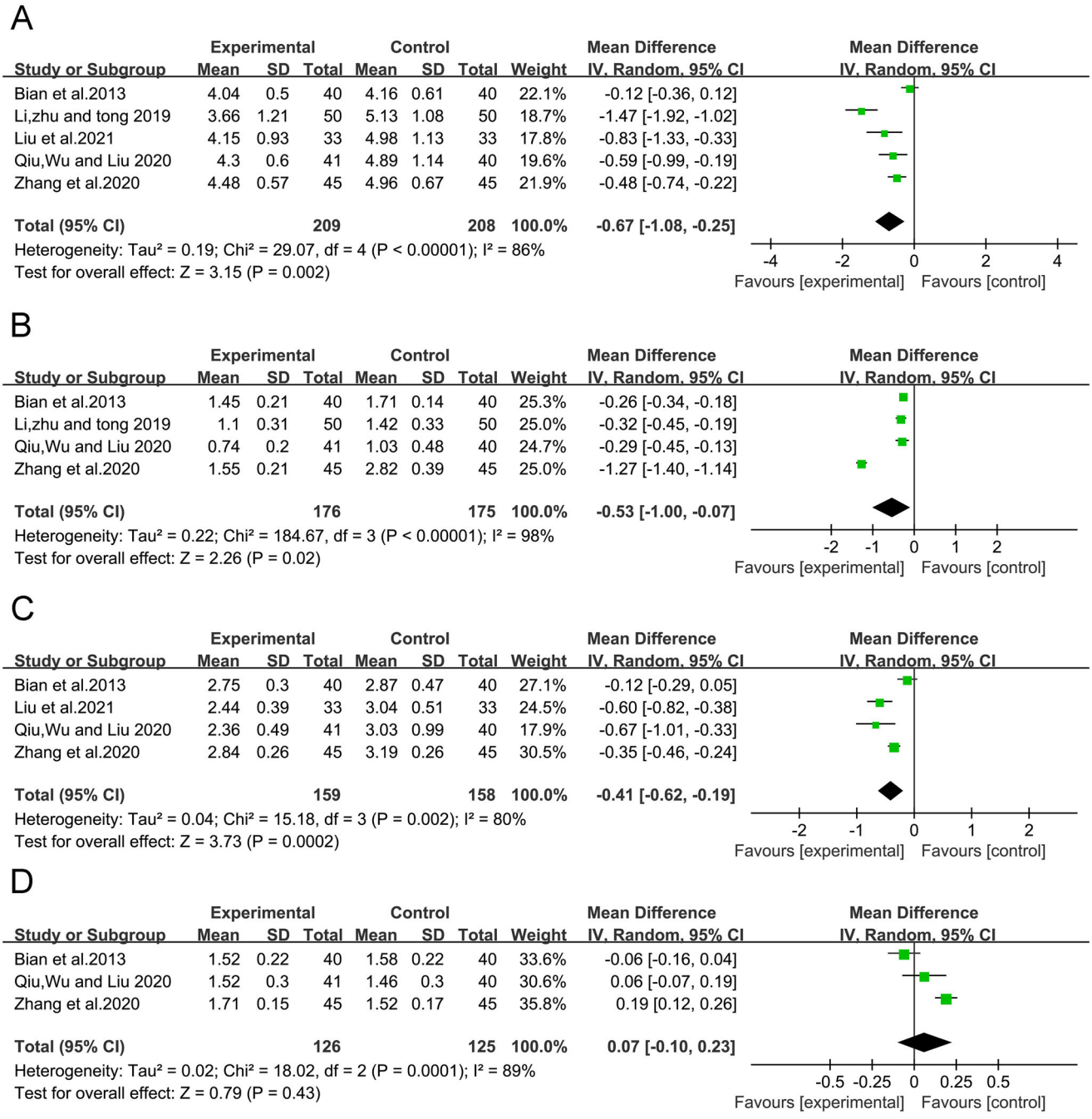

Figure 6. Meta-analysis of CMH on endocrine therapy-induced dyslipidemia of patients with HR + breast cancer (A: TC, B: TG, C: LDL, D: HDL).

by TG). However, due to unexplained high heterogeneity and/or the limited number of included studies, accurate conclusions cannot be drawn regarding the effect of CMH on B-CTX, TC, and LDL in patients with HR(+) breast cancer.

Regarding the evaluation of menopausal symptoms, the levels of E2, FSH, LH, endometrial thickening, and Kupperman score were presented as continuous data. Due to the significant heterogeneity, subgroup analyses were conducted based on TCM breast cancer therapy principles, which primarily include two aspects: strengthening the body (Bu Shen) or a combination of strengthening and removing pathological products (Bu Shen shu gan).

Bu Shen CMH is believed to regulate hormones such as E2 and FSH (Cao et al. 2021), which may impair the efficacy of endocrine suppressive therapy in patients with HR(+) breast cancer. However, this study showed that increased CMH treatment did not affect E2 levels. Subgroup analysis showed that E2 levels were stable, with no significant decrease in E2 levels in either Bu Shen and Bu Shen shu gan CMH subgroups. The heterogeneity was low among subgroups, which suggested that different principles of CMH treatment may be the main factor leading to the heterogeneity of E2 levels; however, Bu Shen shu gan CMH did not affect the FSH levels, while Bu Shen CMH did. However, it is worth noting that the subgroup of Bu Shen also showed high heterogeneity, indicating that other factors were affecting the heterogeneity. Although the meta-analysis revealed significant differences in the LH level, endometrial thickening, and Kupperman score, an

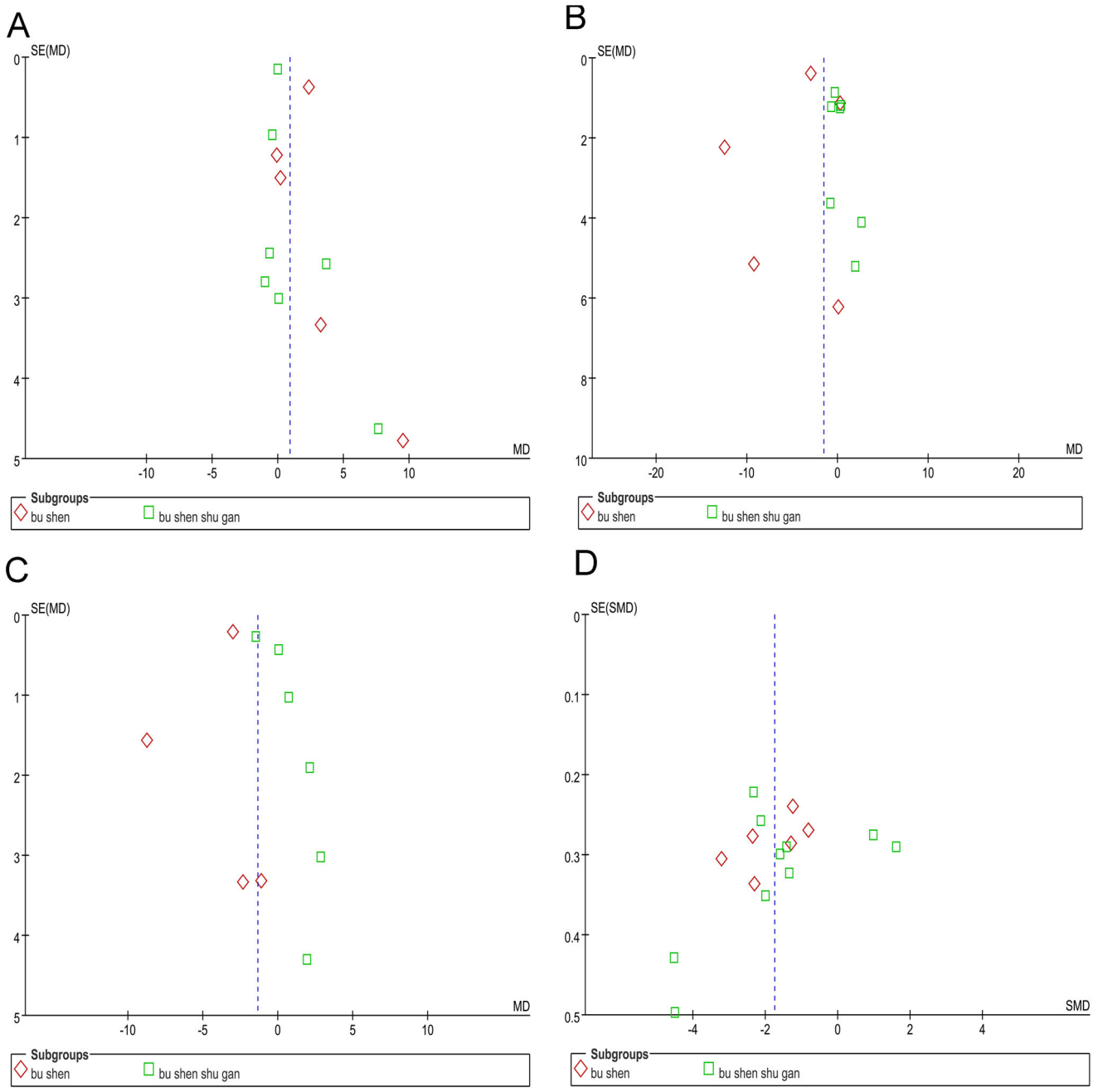

Figure 7. Funnel plot of the studies that investigated menopausal symptoms (A: E2, B: FSH, C: LH, D: Kupperman score).

accurate conclusion cannot be drawn due to high heterogeneity and/or the limited number of included studies.

Limitations

This study has several limitations. First, the overall quality of the included studies was poor, as most trials neglected to specify the allocation concealment method and the blindness of participants and assessors, resulting in an uncertain or high risk of performance and selection bias, which may compromise the applicability of the results. In addition, most studies did not follow up with participants, resulting in unclear long-term effects of CMH on endocrine therapy-induced side effects in patients with HR(+) breast cancer. Second, all research on CMH was conducted in China and published in Chinese, which makes it difficult for other countries to recognize the effect of CMH. Further studies on the impact of CMH published in English are needed. Third, although a subgroup analysis was conducted based on TCM treatment theory, there was still high heterogeneity in the FSH, LH, and Kupperman scores. The main reason for the heterogeneity among the studies was the diversity and complex description of CMH interventions. Therefore, it was not possible to compare the dosage and duration of CMH.

Conclusions

As an adjuvant treatment for patients with HR(+) breast cancer, CMH can alleviate bone loss and decrease TG levels. However, more well-designed, large-sample, multicenter randomized controlled studies are needed to investigate the impact of CMH on

reducing endocrine therapy-induced side effects, including bone loss, menopausal symptoms, and dyslipidemia in patients with HR + breast cancer.

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