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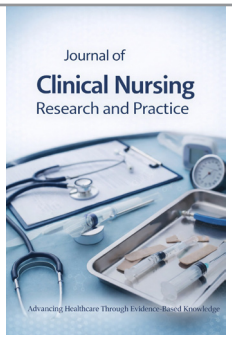
Meta-analysis



Cardiometabolic Risk in Women with Premature Ovarian Insufficiency: A Systematic Review and Meta-analysis

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Keywords
premature ovarian insufficiency; cardiometabolic; cholesterol; triglyceride; HDL-C; LDL-C; glucose; insulin; SBP; DBP

Abstract

Background: *Premature ovarian insufficiency (POI) is defined as a reproductive endocrine syndrome, which is considered to be associated with cardiometabolic risk due to early deficiency of estrogens. Nevertheless, current studies fail to reach a consensus, and systematic reviews and meta-analysis are required to quantify the relevance of these longitudinal studies.*

Objective: *To systematically evaluate optimal evidence regarding the association between POI and cardiometabolic risk factors.*

Methods: *By searching PubMed, EMBASE, Web of Science to determined the eligible studies comparing the cardiometabolic risk factor among women with POI and healthy control, started on August 15, 2021 and no search date restrictions. Data was conducted by random effects model and reported as standardized mean difference (SMD) with 95% confidence intervals (CI).*

Results: *The meta-analysis showed that women with POI had statistically significant increased level of total cholesterol (SMD=0.48, 95%CI (0.31,0.65)), triglycerides (SMD=0.18, 95%CI (0.07,0.30)), low-density lipoprotein cholesterol (SMD=0.41, 95%CI (0.21,0.61)), blood glucose (SMD=0.40, 95%CI (0.17,0.63)), insulin (SMD=0.34, 95%CI (0.02,0.66)) compared with control women. While there was no statisticly difference in high-density lipoprotein cholesterol (SMD=0.08, 95%CI (-0.14,0.03)), systolic blood pressure (SMD=0.03, 95%CI (-0.18,0.23)), diastolic blood pressure (SMD=0.01, 95%CI (- 0.26,0.28)) and incidence of metabolic syndrome (OR=2.51, 95%CI (0.6,10.47)) between women with and without POI. Heterogeneity was significantly reduced after subgroup analysis based on geographic distribution. Sensitivity analysis suggested all outcomes were relatively stable. Begg's funnel plot analysis indicated no publication bias for all factors except of LDL-C (P=0.036).*

Conclusions: *There was higher presence of cardiometabolic risk factors in women with POI. These adverse changes of cardiometabolic indicators can prompt clinicians to focus on cardiometabolic risk in POI women earlier rather than until the onset of long-term complications, so as to facilitate the initiation of intervention and HRT treatment timely.*

Introduction

Premature ovarian insufficiency (POI) is defined as a reproductive endocrine syndrome characterized by hypergonadotropic hypoestrogenic amenorrhea [1] due to ovarian dysfunction in women younger than 40 [2]. It is estimated that approximately 1% at age 40 and about 0.01% at age 20 of the women are diagnosed by POI [3,4]. The etiology of POI is heterogeneous, ranging from spontaneous or idiopathic development to specific reason including chromosomal abnormalities, autoimmune diseases, infections or iatrogenic factors (surgery, radiation, and chemotherapy) [5,6]. On account of depletion of follicles and hypoestrogenism, POI women present to clinical manifestations of infertility and perimenopausal related symptoms, accompanied by an increased risk of long-term comorbidities, including cardiovascular disease (CVD), genitourinary symptoms (vaginal dryness, dyspareunia), osteoporosis, neurological impairment [6,7]. Premature ovarian insufficiency was formerly known as primary ovarian failure (POF), both belong to ovarian dysfunction but are distinct[6,8,9]. POI is characterized by irregular menstrual cycles but have the potential for spontaneous pregnancy occasionally, yet the women with POF usually manifests as amenorrhea with decreased sex hormone levels drop to menopausal state, and can never be pregnant spontaneously. POF is generally considered to be the terminal stage of POI [6;10].

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Cardiometabolic syndrome is a cluster of metabolic and cardiovascular risk factors, involveing pathological processes such as atherosclerotic dyslipidemia, insulin resistance, as well as endothelial dysfunction, increaseing the morbility of cardiovascular disease and type 2 diabetes(T2MD) [11,12], which are prominent cause of death among elderly women worldwide [13,14]. Substantial evidence have showed that adverse lipid profiles including elevated serum levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C) , as well as impaired glucose tolerance, insulin resistance and hypertension are risk factors for cardiometabolic disease. In general, women present an adverse glucolipid metabolic profile due to perimenopausal changes in estrogen levels, it is also worth noting that premature cessation of ovarian function may lead to earlier or more severe cardiometabolic alterations in women with POI. A recent research from Australia showed that women with POI at age 60 had a 3 times higher risk of developing multimorbidity including cardiometabolic diseasessuch as T2MD, CVD and stroke than normal menopausal women [15]. Similarly, privious evidence indicated that POI patients had a 53% higher risk of developing diabetes than women aged >45 years at menopause, from a meta-analysis involveing 21,664 women with diabetes [16]. Early menopause women have approximately 30% higher prevalence of hypertension than women of normal menopause age [17].

The potential mechanism underlying the increased risk of cardiometabolic disease in women with POI remains to be further investigated, and an assessment of differences in metabolic profiles between POI patients and premenopausal age-matched control women may provide convincing evidence for this mechanism. However, the findings so far on the cardiometabolic characteristics of POI patients remain controversial. In a case-control study pointed out that level of lipids and glucose and diabetes prevalence were similar between POI women and healthy controls, and no evidence of early atherosclerosis was found in women with POI [18]. While recently research compared the metabolic profiles of women with POI and age-matched control women, and the results suggested that increased concentration of serum triglyceride and glucose but decreased levels of LDL-C and HDL-C in POI patients [19].

Therefore, the aim of this meta-analysis was to systematically evaluate optimal evidence regarding the association of POI with cardiometabolic risk, and reviewed the role of lipids in cardiovascular pathogenesis, the protective effect of estrogen and receptors on maintaining cardiometabolic health, and the application of hormone replacement therapy (HRT) in POI women.

Material and methods

Study design

This meta-analysis was guided by Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) guidelines [20] and study protocol had registered in PROSPERO (CRD42022320318).

Inclusion and exclusion criteria

Cohort studies, case-control studies and cross-sectional study comparing cardiometabolic risk factors (TC, TG, LDL-C, HDL-C, glucose, insulin, blood pressure) or reporting the incidence of metabolic syndrome between women with and without POI were eligible for this meta-analysis. All participants were not receiving hormone replacement therapy (HRT) and without cardiovascular or endocrine diseases. Search languages are limited to English. According to the European Human Embryology and Reproduction (ESHRE) guidelines, the diagnostic criteria for POI are as follows [1]: women under the age of 40 have at least 4 months of oligo/amenorrhea, elevated serum concentration of follicle-stimulating hormone (FSH) > 25 IU/L detected with an interval of more than 4 weeks. Intervention studies, reviews, conference abstracts, literature with incomplete data were excluded. To maintain homogeneity of the study population, only patients diagnosed with spontaneous or idiopathic etiology of POI were involved. POI caused by iatrogenic or chromosomal abnormalities or autoimmune were unqualified.

Literature search

By searching PubMed, EMBASE, Web of Science to determine the eligible studies comparing the cardiometabolic risk factor between women with and without POI. References in review or original literature were manually searched for additional qualified literatures. Using the following keywords combined with Boolean logic operation for retrieval ‘premature ovarian insufficiency’ OR ‘premature ovarian failure’ OR ‘premature menopause’ AND ‘lipid’ OR ‘cholesterol’ OR ‘triglyceride’ OR ‘low-density lipoprotein cholesterol’ OR ‘high-density lipoprotein cholesterol’ OR ‘glucose’ OR ‘insulin’ OR ‘blood pressure’ OR‘cardiovascular’ OR‘cardiometabolic’ OR‘metabolic’ OR‘metabolic syndrome’ . No search date restrictions, search started on August 15, 2021, with a last update search on April 25, 2022. The detailed search strategies are presented in Supplementary Table 1.

Data extraction and quality assessment

Use standardized data tables to extract the following: (1) Basic information and baseline characteristics of included studies: first author, publication time, country, study design, as well as age and BMI of case and control groups; (2) Data of cardiometabolic risk factors (mean and standard deviation or other data that can be transformed), and the events of metabolic syndrome. The retrieval process and data extraction were carried out independently by two authors (Dr. Yu and Dr. Wu), and in the event of disagreements, a third author (Dr Fu) participated in consultation until an agreement was reached. The methodological quality of all included studies was assessed by the Newcastle- Ottawa Scale (NOS), the more the number of stars obtained, the higher the quality of the literature. Summary scores were assigned for low-quality (≤4), moderate-quality (5- 7), and high-quality (≥7) studies. The quality assessment for each study was conducted independently by two researchers (Dr. Yu and Dr. Wu).

Statistical analysis

The mean and standard deviation (SD) were extracted from continuous data, and the number of events and total sample size were collected for dichotomous data. It is specifically stated that the median and interquartile range (IQR) was presented for continuous variables in studies can convert to Mean and SD with optimal formulation following Cochran's recommendations [21-23], and then weighted the mean for each study according to sample size. Considering the differences in detection method and included populations, the results of meta-analysis for continuous variables are reported as standardized mean difference (SMD) with 95% confidence intervals (CI); dichotomous variables are presented as odds ratios (OR) with

95% confidence intervals (CI). The degree of heterogeneity of the included studies was quantified using the I2 statistic. If P<0.05 and I2>50% were considered significant heterogeneity, a random- effects model was applied; otherwise, a fixed-effects model was selected. Subgroup analyses were performed based on geographic distribution to explore possible sources of heterogeneity. For heterogeneity not explained by subgroup analysis, create a Galbraith plot to explore outliers far from the regression line. For heterogeneity not explained by subgroup analysis, create a Galbraith plot to explore outliers far from the regression line. Publication bias was detected by the Begg's funnel plot. Sensitivity analysis was executed to test the stability of the results through eliminating single study respectively. The test level of the meta-analysis was set to α=0.05. Data analysis was conducted by State 15.0.

Results

Study selection and NOS assessment

A total of 2350 literatures were initially identified by searching electronic databases, 1248 irrelevant literatures and 346 duplicate literature were further eliminated through reading titles and abstracts. Finally, 21 studies were considered eligible in this meta- analysis by carefully evaluated full-text. Of particular note is that one literature fail to extract the data of idiopathic POI due to the inclusion of other etiologies [24], another studies were disqualified because POI patients received hormone therapy [25]. The specific literature screening process is shown in the flowchart (Figure 1).

Of the included studies, 18 were cross-sectional studies and 3 were prospective studies, published between 1996 and 2022 and mainly derived from Turkey [26-34], Poland [35,-38], Netherlands [18;39;40],China [19;41], Greece [42], and Iran [43], with a total of 1635 POI women and 1836 control women. The NOS scores of the included literatures ranged from 5 to 8 stars, of which there were 19 literatures with ≥6 stars, indicating that the overall research quality was high. The baseline data and characteristic of the included studies are shown in Supplementary Table 1 and Supplementary Table 2. Details of NOS scores for all included studies can be found in Supplementary Table 3.

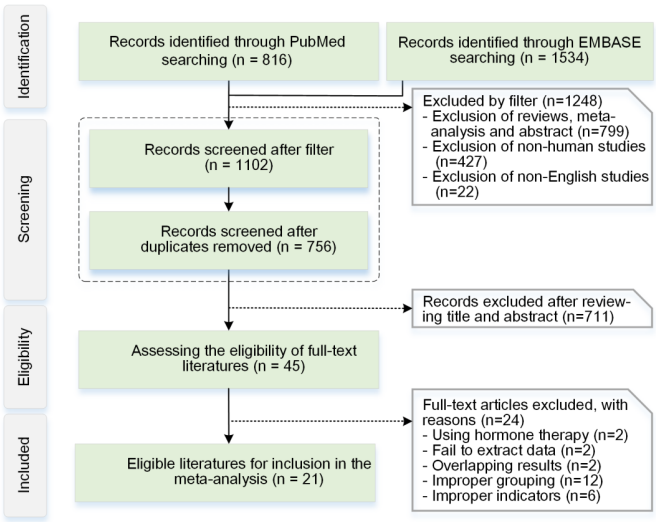

Figure 1. *Flowchart of included studies on cardiometabolic risk in women with POI*

Outcomes

All cardiometabolic indicators showed significant heterogeneity (I2>50%, P<0.05), so a random effect model was conducted for analysis. The meta-analysis showed a statistically significant higher concentration of TC (SMD=0.48, 95%CI (0.31,0.65), P=0.000), TG (SMD=0.18, 95%CI (0.07,0.30), P=0.002), LDL-C (SMD=0.41, 95%CI (0.21,0.61), P=0.000), glucose (SMD=0.40, 95%CI (0.17,0.63), P=0.001), insulin (SMD=0.34, 95%CI (0.02,0.66), P=0.038) among POI group compared to control group (Figure 2ace; Figure 3c). However, there was no statistically differentin in HDL-C (SMD=0.08, 95%CI (-0.14,0.03), P=0.476), SBP (SMD=0.03, 95%CI (-0.18,0.23), P=0.775) and DBP (SMD=0.01, 95%CI (-0.26,0.28), P=0.923) among women with POI compared to control women (Fig. 2g; Fig. 3eg). No evidence found for differences in the rate of Mets (OR=2.51, 95%CI (0.6,10.47), P=0.208) between women with and without POI (Figure 4).

Subgroup analysis was performed to explore sources of heterogeneity. As most studies were derived from Turkey (n=9), subgroup analysis was conducted according to geographic factors (Turkey subgroup and other countries subgroup). The results showed that the direction and influence of TC, LDL-C, and glucose in the Turkish subgroup and other country subgroups were consistent with the total effect size, and the heterogeneity was significantly decreased. TG and HDL-C were only statistically elevated in the Turkish subgroup, and insulin was only statistically significant in the other country subgroups. While there was no difference in SBP and DBP between Turkish subgroup and other country subgroups, which consistent with the total effect size. Overall, the heterogeneity of all cardiometabolic indicators were significantly reduced with the exception of HDL-C after subgroup analysis (Table 3). Subgroup analysis unable to identify the source of heterogeneity for HDL-C. Therefore, Galbraith plot was further conducted and exclusion of seven outliers [19;29;31-35;44] made a decrease in the I2 statistic from 86.7% to 23.1% (P=0.231) , and the direction of point estimate value (SMD=0.13, P=0.000) was consistent with the original total effect size (Supplementary Figure 1). Subgroup analysis of metabolic syndrome data was unable to conducted due to only one literature on other country subgroups.

Sensitivity analysis by respectively removing single study suggested the results of meta-analysis were relatively stable (Fig. 2bdfh; Fig. 3bdfh). The Begg's test funnel plot indicated there was no significantly publication bias in the studies on TC (P=0.33), TG (P=0.133), HDL-C (P=0.31), Glu (P=0.916), insulin (P=0.183), SBP (P=0.183), DBP (P=0.183), while a certain publication bias in the studies on LDL-C (P=0.036) (Supplementary Figure 2). The number of studies on Mets is too small to reliably evaluate publication bias by Begg's funnel plot.

Discussion

Main findings

This systematic review and meta-analysis were performed to clarify the association between premature ovarian insufficiency and cardiometabolic risk as a result of conclusions were heterogeneous in previous studies. The results of meta-analysis showed that serum concentrations of TG, TC, LDL-C, glucose and insulin among POI women were statistically higher than those without POI, indicated these elevated levels of cardiometabolic indicators were associated with POI and may be moderate risk factors for the occurrence and development

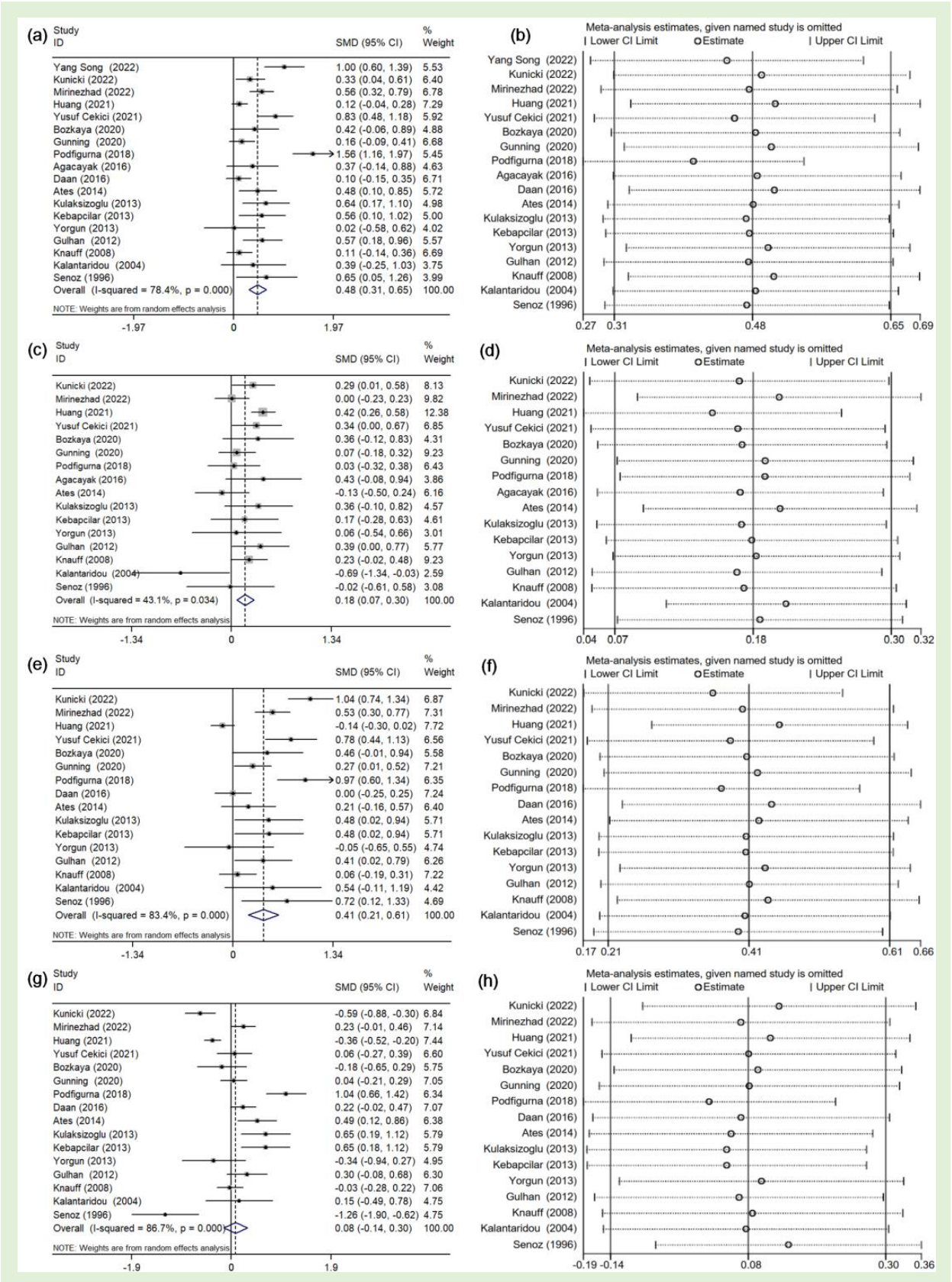

Figure 2. *Forest plots and Sensitivity analysis for total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) concentration in POI women compared with control women. (a) Forest plot for TC;(b) Sensitivity analysis for TC;(c) Forest plot for TG;(d) Sensitivity analysis for TG; (e) Forest plot for LDL-C;(f) Sensitivity analysis for LDL-C;(g) Forest plot for HDL-C;(h) Sensitivity analysis for HDL-C;*

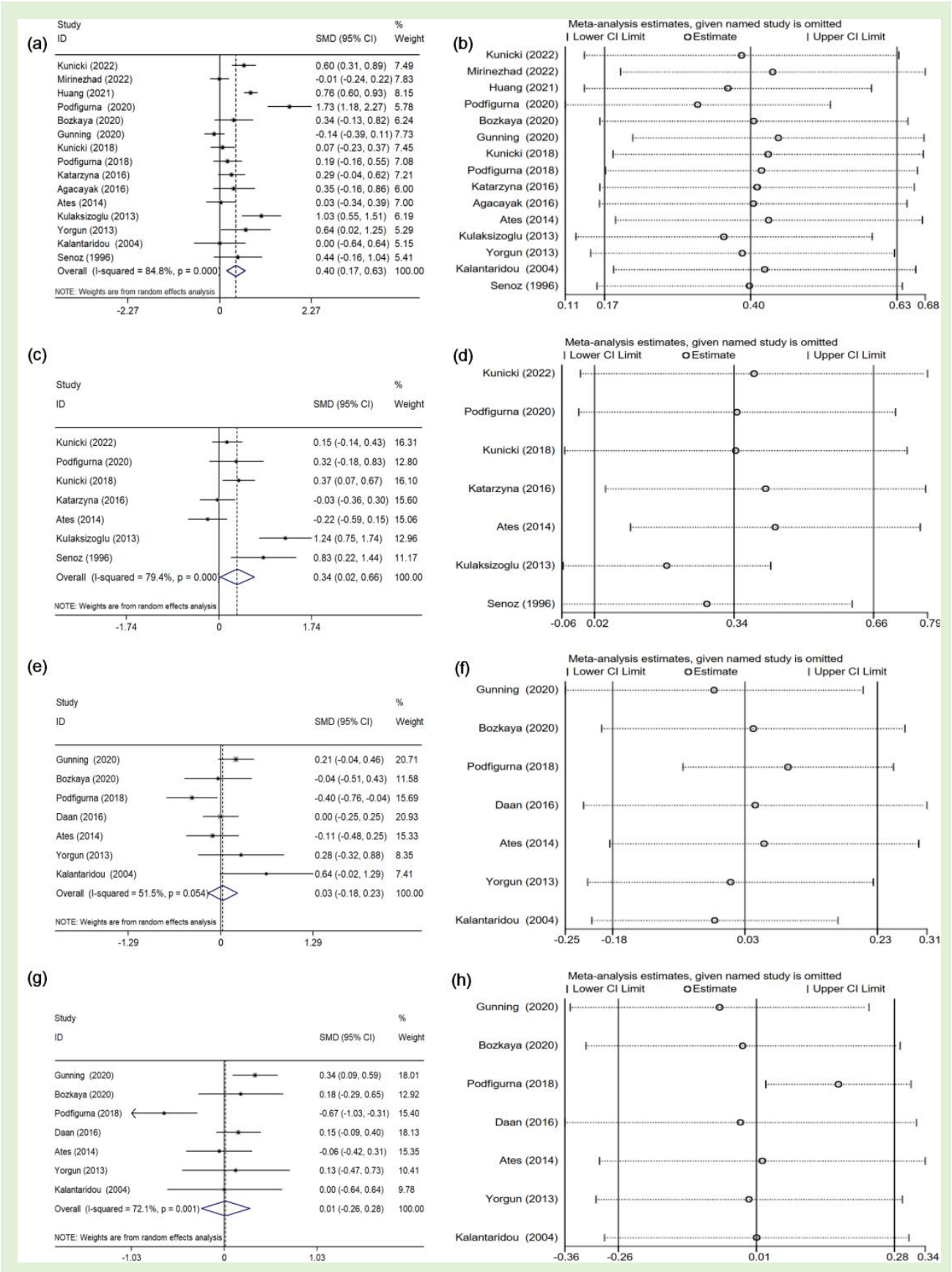

Figure 3. *Forest plots and Sensitivity analysis for glucose (Glu), insulin (INS), systolic blood pressure (SBP) and diastolic blood pressure (DBP) level in POI women compared with control women. (a) Forest plot for Glu;(b) Sensitivity analysis for Glu;(c) Forest plot for INS;(d) Sensitivity analysis for INS; (e) Forest plot for SBP;(f) Sensitivity analysis for SBP;(g) Forest plot for DBP;(h) Sensitivity analysis for DBP.*

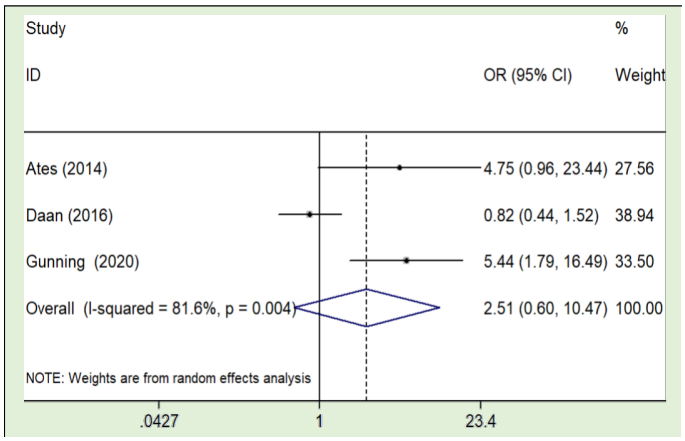

Figure 4. *Forest plots for metabolic syndrome in POI women compared with control women*

of cardiometabolic disease among POI. However, there was no evidence to explain the SBP, DBP and HDL-C as the risk factors for POI since no significant difference between the two groups. Sensitivity analysis showed that SMD values of all cardiometabolic indicators fell within the 95% confidence interval of the original effect size, indicating that results of meta-analysis were relatively stable.

Subgroup analysis was conducted based on geographic distribution (Turkey subgroup and other countries subgroup) due to Turkey (n=9) was the country with the highest proportion among included studies. The results indicated that the direction and influence of most indicators were consistent with the original effect size after subgroup analysis, and the heterogeneity of TC, TG, LDL-C, SBP, and DBP in the Turkish subgroup was significantly reduced (I2=0%). This can be reasonably explained that Turkey belongs to Asia, while most of the remaining studies are from European countries such as Poland and the Netherlands. There are essential differences between Asians and Europeans in terms of race and ethnicity, which affects individual obesity and body mass index (BMI). Previous studies have shown that under the same BMI, the incidence of diabetes in Asian population is higher than that in European population, and East Asians have higher body fat content and a tendency toward visceral adiposity [45]. Similarly, this meta-analysis also showed that the serum level of lipids, glucose and insulin in the Turkish subgroup were higher than those of the other country subgroups. Therefore, it is logical to consider geographic distribution and ethnic difference as potential factors affecting the heterogeneity.

Interpretation in the context of other evidence

Adverse lipid profiles occur during menopause due to changes in sex hormones [46]. A previous meta-analysis comparing lipid profiles in 68,394 premenopausal and 46,261 postmenopausal women showed a higher concentration of TC, TG and LDL-C in postmenopausal women, while no difference in HDL-C levels, which was consistent with our result of meta-analysis. Evidence suggested that women with premature menopause had a statistically increased risk of non-fatal cardiovascular disease incidents before aged 60 compared with menopausal women aged 50-51, so age at menopause may also be regarded as a vital factor in the risk stratification of CVD in women [47]. The British Biobank cohort study showed an increase in the overall prevalence of CVD for both surgical POI (HR1.87,95%CI1.36-2.58) and spontaneous POI (HR1.36,95%CI 1.19-1.56) after fully adjusted models [48]. Spontaneous POI is related to elevated risk of various CVD, involving coronary heart disease, aortic stenosis, stroke, as well as venous thromboembolism, and the risk of CVD gradually increases with the younger menopausal age [48]. Dyslipidemia is well-established to be a primary risk factor for different cardiovascular diseases, and in addition to the unfavorable lipid profile in POI patients, risk factors related to the evolusion of CVD like abnormal blood glucose metabolism, insulin resistance, and endothelial dysfunction have also been observed [49]. Early menopause is related to a higher risk of T2DM, as presented in a prospective case-cohort study from the InterAct , the hazard ratio for T2DM in women with POI was 1.32 (95%CI 1.04-1.69) compared with women at menopause age 50-54 years during 11 years follow-up observation period [50]. Although our study suggested no significant differences in systolic and diastolic blood pressure between women with and without POI, recent meta-analysis indicated that the prevalence of hypertension in women with early menopause was approximately 30% higher than women with normal menopause [17], and hypertension can further increase the risk of cardiometabolic disease, so it is still required to pay attention in POI women.

The metabolic syndrome (MetS) is a group of cardiometabolic risk factors including glucose intolerance, obesity, hypertension, and dyslipidemia [47], the patients who affected by MetS are at increased risk of CVD and T2DM [51]. Meta-analysis on global prevalence showed higher prevalence of MetS in postmenopausal women than premenopausal women at the same age [52], and this risk association appears to apply to women with POI as well. Ates et al indicated that the prevalence of Mets in women with POI and age and BMI matched controls was respectively 14.3% and 3.4% in a case-control study [29]. However, this meta-analysis suggested the rate of Mets in the POI women was increased but not statistically different. Due to the small number of included Mets studies, more prospective studies are required to confirm this association. It is worth noting that the pathological mechanisms behind Mets, namely dyslipidemia, insulin resistance and glucose intolerance, are mutually reinforcing. Insulin plays a key role in anti-lipolysis and stimulation of lipoprotein lipase. When insulin resistance occurs, more fatty acids are produced to inhibit the anti-lipolytic effect of insulin [53], while the increased flow of free fatty acids to the liver will increase the synthesis of triglycerides [54], hypertriglyceridemia can further trigger a reduction in HDL-C levels, leading to increased removal of HDL-C from the blood circulation due to a decreased in lipoprotein core cholesteryl esters [55,56]. In conclusion, abnormal glucolipid metabolism and insulin resistance lead to a significantly increase in the incidence of CVD and T2DM, mainly attribute to the lack of protective effects of estrogen due to ovarian failure [57,58]. It is worth further researching the mechanism of estrogen and receptors.

Effects of estrogen and receptors on cardiometabolism

Decreased estrogen levels and abnormal expression of estrogen receptors (ERs) as well as altered lipid profiles are one of the pathological mechanisms in perimenopausal and postmenopausal atherosclerosis [59]. The beneficial impact of estrogen on many organ systems have been widely established, containing conductively regulation of hepatic lipid metabolism and various lipoprotein levels. Previous studies have shown that the protective effect of E2 was considered to be achieved by

reduction of LDL-C, increasing of HDL-C, lightly decreasing atherosclerosis and increasing post ischemia reperfusion [51]. Many biological functions of triglycerides, cholesterol and hepatic fatty acids, and the gene expression linked to lipid metabolism and CHD are regulated by endogenous estrogens and ERs, including ERα, ERβ, and G protein conjugated estrogen receptor (GPER) [60,61]. Estrogen reduces the activity of hepatic lipases and increases the production of high-density lipoprotein and HDL-lipoprotein (apo AI) in the liver, which may account for the elevated level of HDL-C. In the meantime, estrogen trigger the clearance of LDL from the blood circulation by upregulating LDL receptors and reduces TC concentration mainly by reducing LDL-C levels. Additionally, Estrogen has advantageous effects on glucose metabolism by reducing abdominal fat deposition, increasing lipid oxidation and improving insulin sensitivity [62]. Therefore, postmenopausal women increase bone marrow-derived adipocytes by reason of estrogen deprivation, resulting in increased visceral fat. Protein lipase further enhances the lipolysis of visceral fat to generate excess free fatty acids, triggering metabolic disorders along with insulin resistance [63]. Many functions of estrogen receptors (ERs) in mediating cardiometabolic risk have been demonstrated in animal studies. The loss of ability of estrogen to prevent hepatic steatosis was observed in ERα knockout mice due to loss of ERα receptors in hepatocytes, suggesting that estrogen-receptor signaling acts on the liver to reduce TG levels [64,65]. In mice with atherosclerosis induced by feeding, systemic deletion of GPER accelerated atherosclerosis and increased LDL-C levels [65]. Reduced glucose oxidation, increased insulin level and obesity were found in transgenic mice (ArKO mice) inactivated with aromatase, which was critical for E2 synthesis, certifying the importance of estrogen in glucose metabolic homeostasis and obesity state [66].

Application of hormone replacement therapy in POI

Untreated POI is related to shorten life expectancy, primarily owning to cardiovascular disease [1], early initiation of hormone replacement therapy (HRT) is recommended for women with POI. A cross-sectional study indicated that women with POI had a 0.18%-0.2% increased risk of CVD events every year in the absence of estrogen exposure, conversely, with estrogen exposure, the risk of CVD events was reduced by 0.15-0.16% every year. Estrogen exposure was inversely associated with CVD risk and serum concentration of non-HDL-C [67]. Clinical data suggested that HRT was protective in preventing menopausal symptoms when used in women approaching the menopausal transition, but was ineffective or had side effects when the HRT was initiated after menopause [68,69]. ESHER guidelines still strongly recommend that early HRT in POI women should be persistent at least until the mean age of natural menopause, despite the lack of longitudinal data, because a large number of studies so far have consistently illustrated that HRT can effectively relieve menopausal symptoms and complications caused by estrogen deficiency such as osteoporosis, dyslipidemia and cardiovascular disease [70,71]. Judgment for treatment requires understanding of individual preferences and assessment of potential risks, such as symptom severity, family history of cancer, cardiovascular and cerebrovascular disease, osteoporosis and deep vein thrombosis [72,73]. 17-βestrogen is preferred over ethinyl estradiol or conjugated equine estrogen for choice of HRT. Addition of progestogen counteracts the continued proliferative effect of estrogen on the endometrium, micronized natural progesterone is associated with better glycemic metabolism, cardiovascular and udder safety profile [1,74]. Oral and transdermal administrations have similar effects, while transdermal administrations have a lower risk of venous thrombosis [75]. Follow-up is necessary after HTR aiming to assess adverse effects of HRT and to inspect effectiveness and compliance of therapeutic regimen. In conclusion, individualized therapy is the key to management in patients with POI, with the aim of maximizing efficacy and reducing clinically relevant risks. The role and mechanism of estrogen warrants further investigation to elucidate the effect of HRT on cardiometabolism.

Strengths and limitations

We provide a unique contribution to the literature demonstrating a higher cardiometabolic risk factors in POI patients compared to healthy women. Although previous studies have used relative risks (RRs) and odds ratios (OR) as effect sizes to report meta-analysis of POI and the risk of CVD, ischemic heart disease, stroke, diabetes, and hypertension[16,17,76], our study still remains valuable and necessary. Because the changes in serum concentrations of cardiometabolic indicators precede the incidence of cardiometabolic diseases, this changing trend will prompt clinicians to pay attention to cardiometabolic risk in POI women earlier, rather than until long-term complications arise, so as to facilitate the initiation of intervention and HRT treatment timely. In addition, the potential mechanism underlying the increased prevalence of cardiometabolic disease in women with POI remains to be further investigated, and an assessment of differences in cardiometabolic profiles between POI and premenopausal control women may provide crucial clues for this mechanism. However, there are certain limitations should also be mentioned. Firstly, the high heterogeneity in each cardiometabolic risk factors may be derived from the combination of clinical heterogeneity due to racial differences in the included populations and methodological heterogeneity due to incomplete matching of age and BMI between case and control groups in some studies. Secondly, data from prospective cohort studies are lacking to assess the causal relationship between POI and cardiometabolic risk factors. More prospective studies with large samples and multiple centers to evaluate this association are warranted in the future. Finally, some studies did not indicate whether the case and control populations were matched for BMI and age, and we fail to conduct more subgroup analyses and regression analyses based on BMI and age to explore influence factors of heterogeneity.

Conclusions

In conclusion, this study demonstrates that increased levels of cardiometabolic risk factors in women with POI including TC, TG, LDL-C, glucose, and insulin, which are presage to development of abnormal lipid metabolism, glucose intolerance and insulin resistance. These unfavorable changes are partially attributed to deficient estrogen triggered by ovarian dysfunction, potentially increasing future risk of CVD, diabetes and metabolic syndrome. The adverse trend might prompt clinicians to focus on cardiometabolic risk factors in POI women earlier rather than until long-term complications arise, so as to facilitate the initiation of intervention and HRT treatment timely. Therefore, this study is a meaningful indication of elevated cardiometabolic risk in women with POI, and provides a valuable rationale for the mechanism by which POI increases the incidence of cardiometabolic disease.

Competing interests

The authors declare that they have no conflict of interests.

Availability of data and materials

This review article is based on findings from relevant published studies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Acknowledgements

Not applicable.

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