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Review Article

Association of ESR1 and ESR2 Gene Polymorphisms with Metabolic Syndrome in Peri- and Postmenopausal Women: A Systematic Review

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ABSTRACT

Metabolic Syndrome (MetS) encompasses central obesity, insulin resistance, dyslipidemia, and hypertension, collectively increasing risks of cardiovascular disease and type 2 diabetes. Menopause exacerbates susceptibility to MetS due to hormonal changes and genetic factors. Estrogen receptors ESR1 and ESR2 are pivotal in estrogen signaling and metabolic regulation, and their gene polymorphisms may affect metabolic health in peri- and post- menopausal women. This systematic review evaluates studies up to March 2025 that examined associations between ESR1 and ESR2 Single Nucleotide Polymorphisms (SNPs) and MetS or its components in peri-/post-menopausal women. Fifteen observational studies met the inclusion criteria. ESR1 variants rs9340799 (XbaI) and rs2234693 (PvuII) were consistently associated with higher MetS prevalence, obesity markers, and insulin resistance. ESR2 SNPs (such as rs3020449, rs1256049, rs4986938) showed variable associations dependent on population background and interaction with hormonal status. Overall, ESR1 polymorphisms appear to have a stronger influence on metabolic disturbances during menopause than ESR2, particularly when modulated by lifestyle, ethnicity, and hormonal levels. These findings underscore the importance of integrating precision medicine approaches to improve women's metabolic health

Keywords Metabolic syndrome, ESR1, ESR2, Menopausal women, Precision medicine.

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INTRODUCTION

Metabolic Syndrome (MetS) is a group of related cardiovascular risk factors including central obesity, glucose intolerance, dyslipidemia, and hypertension that collectively raise the risk for type 2 diabetes and cardiovascular disease. The prevalence of MetS rises dramatically during the menopause, where it is estimated that the number of postmenopausal women affected globally amounts to some 45%. This observed increase is attributable to both hormonal changes and genetic susceptibility as critical variables in the disturbance of metabolic balance at this life stage (Goulart *et al*., 2009). Estrogen serves as a key regulator in women for the distribution of the adipose tissue, insulin sensitivity and lipid metabolism. The fall in its level in menopause is directly related to unfavorable changes in the fat deposition, increased inflammation, and the altered insulin action-all of which are symptoms of MetS. Functioning as a modulator of estrogen, the role of estrogen was originally thought to be executed by its two nuclear receptors, estrogen receptor alpha (ERα, encoded by the ESR1 gene) and estrogen receptor beta (ERβ, encoded by the ESR2 gene) (Zhao *et al*., 2018). Both of these receptors have varied tissue distributions and hence monitor metabolic processes in the liver, the skeletal muscle, and the fat tissue as a single collective unit (Kuźbicka *et al*., 2022).

Research has emerged pointing to the fact that some common genetic variations, especially SNPs (single-nucleotide polymorphisms) in the ESR1 and ESR2 genes, may regulate the action of estrogen, thereby either raising or lowering the

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risk and severity of MetS in women. Among these, there are PvuII (rs2234693) and XbaI (rs9340799) in ESR1, which have been closely associated with gene expression, receptor action, and metabolic outcomes. Correspondingly, the implication of the role of several polymorphisms in ESR2, such as rs1256049 and rs4986938 in metabolic and cardiovascular phenotype, has also been studied. However, due to the heterogeneity of the populations, research designs, and MetS' definitions of different studies, the results are not consistent (Ghal *et al*., 2018).

The examination of ESR1 and ESR2 polymorphisms in the context of metabolic disorders is not just an issue of biologically unfolded matters, it is also a central question that has to be answered at the clinical level (Krakowiak *et al*., 2022). The identification of these genotypic traits that expose menopausal women to risk would let preventive medicine be customized suitably and let precision medicine be developed at this critical moment in women's lives (Bai *et al*., 2018). Also, since Hormone Replacement Therapy (HRT) is still uncertain in terms of metabolic risk reduction, a clearer understanding of genetic determinants can help to make therapeutic decisions tailored more precisely (Zhou *et al*., 2018).

Reading the literature, it is observed that there has been no recent systematic review in which the abovementioned findings about the ESR1 and ESR2 polymorphisms and MetS specifically in menopausal women were comprehensively synthesized-an essential point marking the theoretical cooperation of genetics with the endocrine system and the improvement of women's heart health. Thus, this study is aimed at critically examining and summarizing the current evidence of the connection between hand-picked ESR1 and ESR2 gene polymorphisms and the frequencies, components, and severity of MetS in peri and postmenopausal women globally.

Rationale and Scope of the Review

Despite growing evidence linking estrogen receptor gene polymorphisms to cardiometabolic risk, findings remain fragmented and sometimes contradictory due to population heterogeneity, varying diagnostic criteria for metabolic syndrome, and differences in menopausal status classification. Moreover, the menopausal transition represents a critical window during which declining estrogen levels may amplify the phenotypic effects of genetic variation. To date, no recent systematic review has comprehensively synthesized the evidence focusing specifically on ESR1 and ESR2 polymorphisms in peri- and postmenopausal women with metabolic syndrome. Addressing this gap is essential to clarify genetic contributions, identify consistent risk variants, and inform personalized prevention strategies.

Objective of the Review

The primary objective of this systematic review is to critically appraise and synthesize current evidence regarding the role of Estrogen Receptor alpha (ESR1) and Estrogen Receptor beta (ESR2) gene polymorphisms in influencing the risk, prevalence, and components of metabolic syndrome among peri- and postmenopausal women. By evaluating studies that examine genetic associations across diverse populations and accounting for interactions with hormonal and environmental factors, this review aims to clarify the extent to which specific ESR1 and ESR2 variants contribute to metabolic dysfunction during the menopausal transition. Ultimately, the goal is to inform personalized risk stratification and potential prevention strategies targeting cardiometabolic health in this vulnerable population.

This review first outlines the biological relevance of estrogen receptor signaling in metabolic regulation, followed by a systematic description of the literature search methodology. The results are then synthesized thematically according to ESR1 and ESR2 polymorphisms, with emphasis on consistency, population-specific effects, and gene-environment interactions. Finally, the findings are critically discussed in the context of biological plausibility, study heterogeneity, and clinical implications.

METHODOLOGY

This study was conducted as a systematic review of observational studies and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy and Study Selection

A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and EMBASE from database inception to March 31, 2025. The search strategy combined controlled vocabulary terms (MeSH) and free-text keywords related to estrogen receptors, genetic polymorphisms, menopause, and metabolic syndrome. Key search terms included: “ESR1” OR “estrogen receptor alpha”, “ESR2” OR “estrogen receptor beta”, “polymorphism” OR “single nucleotide polymorphism”, “metabolic syndrome”, and “menopause” OR “postmenopausal women”. Boolean operators (“AND”, “OR”) were applied to refine the search. Reference lists of eligible articles and relevant reviews were manually screened to identify additional studies.

To perform the literature review, four major digital databases namely, PubMed, Scopus, Web of Science, and EMBASE were carefully screened through the end of March 2025. The search was a blend of controlled vocabulary (for example, MeSH terms such as "Estrogen Receptor alpha," "Metabolic Syndrome," "Menopause") and ordinary keywords combined by means of the Boolean operators ("AND", "OR", "NOT"). Another strategy that was utilized refers to the thorough inspection of the reference lists of those articles that met the selection criteria as well as reviews on the topic. After the elimination of duplicates, 42 records were checked for title and abstract and also three records from references resulting in a total of 15 studies that underwent full-text examination and eventually 15 studies were determined as evidenced-based-observational studies (case-control, cohort, or cross-sectional) which explored the presence of ESR1 and/or ESR2 gene polymorphisms in menopausal women with the diagnosed metabolic syndrome or any of its components (Figure 1 PRISMA).

Inclusion and Exclusion Criteria

Studies were eligible if they: (i) included peri- or postmenopausal women; (ii) evaluated one or more ESR1 or ESR2 single nucleotide polymorphisms; (iii) assessed metabolic syndrome or its components using recognized diagnostic criteria (e.g., NCEP-ATP III, IDF); and (iv) provided sufficient genetic and metabolic data for analysis.

Exclusion criteria included non-human studies, review articles, editorials, case reports, conference abstracts, studies lacking clear menopausal status classification, or those without relevant genetic data.

Data Extraction

Two reviewers separately collected data from a structured and tested extraction form that was prepared in Excel implementing standardized piloting by one of the authors. Information about the study identifiers (author, year, country), the sample size and menopausal state, the SNP information and methods of genotyping, and the definition of metabolic syndrome, allele/genotype frequencies, effect estimates (odds ratios, mean differences), adjustment for confounders, and weather conditions were included in the data. Any discrepancies were discussed and where necessary, resolved by consulting a third reviewer to ensure consensus and reduce bias.

RESULTS

Characteristics of Included Studies

ESR1 Variants

The ESR1 gene that represents the estrogen receptor alpha has numerous polymorphisms which have been the subject of many studies that aimed to determine their genetic association with Metabolic Syndrome (MetS) in women after menopause (Figure 2). Of these, SNP rs9340799 (XbaI) made itself noticeable by being the most frequently involved in the metabolic risk area (Goulart *et al.*, 2009). In six of the ten studies taken into consideration, covering Chinese, Polish, Egyptian, and Brazilian populations, it was conclusively shown that the G allele of rs9340799 was associated with a higher prevalence of MetS, increased Body Mass Index (BMI), larger waist circumference, higher triglyceride level, and augmented insulin resistance (Zhao *et al.*, 2018). They illustrate the potency of the allele as a risk factor, which is the same across different ethnic groups. Nonetheless, the variability due to race and the place of studies was mentioned by two other studies, conducted in the United States and Sweden, that showed that there was no significant and reliable connection between the G allele and metabolic consequences, which means that the genotype-phenotype relations can be modified by the population in a particular location (Krakowiak *et al.*, 2022).

Aside from there is another frequent polymorphism in the ESR1 gene, rs2234693 (PvuII), that has also been under focus of multiple studies (Kuźbicka *et al.*, 2012). Out of the ten reviewed papers, five studies have confirmed significant associations between the presence of the C allele or carrying the TC or CC genotypes and the show of the indicators of MetS, the prevalence of this syndrome, the development of obesity, etc., particularly in peri-menopausal women (Bai *et al.*, 2013). These results agree with the idea that ESR1 intronic variants are the main

Table 1: Single Nucleotide Polymorphisms (SNPs) in ESR1 and ESR2 genes associated with MetS.

First Author (Year)	Country	Sample Size (Meno/Post-Meno)	SNPs Genotyped	MetS Definition	Key Positive Associations
(Kuźbicka *et al.*, 2022)	Poland	147 post	ESR1 rs2234693, rs6902771; ESR2 rs3020449	IDF	rs2234693 C allele ↑ MetS, ↓ HDL-C
(Zhou *et al.*, 2018)	China	304 post	ESR1 rs2234693, rs9340799; ESR2 rs1256049, rs4986938	NCEP	rs9340799 G allele ↑ MetS, HOMA-IR
(Kuźbicka *et al.*, 2012)	Poland	404 peri/post	ESR1 rs9340799, rs2234693	IDF	rs9340799 GG ↑ MetS in peri-M
(Goulart *et al.*, 2009)	USA	532 post	ESR1 rs2234693, rs9340799; ESR2 rs1271572, rs1256049, rs4986938	NCEP	Null overall
(Ahmed *et al.*, 2022)	Sweden	100 SAT/VAT biopsies	ESR1/ESR2 mRNA + GWAS SNPs	–	ESR1 variants linked to body-fat distribution

factors behind the modulation of metabolic gene expression and receptor expression in the target tissues during the transitional life stage. Although signifying a possible relationship of Estradiol (E2) with these genotypes, in particular, the risk was multiplied when estradiol levels were low, it reinforced the hypothesis of the existence of gene-hormone reactions as the most important thing in the determination of metabolic health of menopausal women (Ahmed *et al.*, 2022) (Table 1).

ESR2 Variants

Contrasting with ESR1, ESR2 genes suffer from a lack of research, and the findings that exist are not in agreement. A typical example of this is the promoter variant rs3020449, which has been identified as the one to watch in several populations (Uzar *et al.*, 2016). One of the best illustrations is a cohort of Poles where the associations were quite strong for rs3020449 with both MetS prevalence and lipid profiles alone that were unfavorable so that the possible regulatory), alongside the possible regulatory nature of the genetic variant within the ESR2 gene influenced metabolic traits due to ESR2 under-expression or silencing (Mazurek *et al.*, 2020). Nevertheless, there was no correlation of this phenomenon with studies conducted in Mongolia and the United States from where it was concluded that the latter two countries remained free of Met... The two coding SNPs of ESR2, namely, rs1256049, (RsaI), and rs4986938, (AluI) were also investigated for their metabolic effects. The results of these studies were found to be highly inconsistent: while in China, two particular genetic studies associated the minor alleles of these SNPs with less favorable lipid indices (for example, a potential increase of LDL cholesterol and a decrease in HDL cholesterol), the majority of the rest Pr.114 of the (the most of the other included) studies that were part of the discussion were unable to identify any relationship that was statistically significant (Chuluun-Erdene *et al.*, 2018) (Table 2).

Gene–Phenotype Pathways

The structural chains that establish among estrogen receptor gene polymorphisms and metabolic syndrome have the potential to operate via several interrelated pathways. In regard to fatness, ESR1-related risk alleles are represented by the variation that is most notably found at intron 1, these are connected with the process of visceral fat accumulation, which is the reason for the increase in waist circumference, thus central diagnostic criteria of MetS. Genotypic makeup may affect local adipocytes to be different in gene expression and to keep more lipids, thus confirming the pre-existing fatness of a woman (Zhou *et al.*, 2017).

As far as the glucose homeostasis subject is concerned, there is a good chance that Estrogen Receptor alpha (ESR1) is changing the situation with the help of the insulin signaling pathway components, for example the insulin receptor substrate. Dragon models were the sources of the data that have strongly supported the above claim by way of the results that were obtained from the studies, which indicate that ERα gene-deleted mice show lower insulin sensitivity and are thus more insulin resistant, and also that as a result, the mice are prone to the problems (e.g. metabolic syndrome) shown by the human being, like for example hyperglycemia and increased fasting insulin (Uzar *et al.*, 2016).

Characteristics of cells such as ERα and ERβ are important players in the metabolism of lipids. The role they play in lipid regulation is connected to the same function, that is to change gene expression and enzyme activity of the different lipoproteins and LDL. As a consequence, the person might experience changes in LDL particles that influence their size and distribution and affect positively or negatively the HDL cholesterol concentrations. The issue of such changes in some receptors over others is the ATP-binding cassette transporters that serve as the ones responsible for the increase in LDL and the decrease in HDL-C. This description outlines various ways in which ESR1 and ESR2 polymorphisms take part in the formation of metabolic syndrome and some of its basic symptoms that are present in menopausal women as well, which are produced by the combination of the environment and the hormone in genes in the women's bodies.

Table 2: ESR1 and ESR2 polymorphisms and their association with metabolic syndrome and related traits in menopausal women.

Gene	SNP	Populations Studied	Key Findings
ESR1	rs9340799 (XbaI)	Chinese, Polish, Egyptian, Brazilian	G allele associated with higher MetS prevalence, increased BMI, waist circumference, triglycerides, and insulin resistance in 6 of 10 studies. Null findings in US and Swedish cohorts.
ESR1	rs2234693 (PvuII)	Various including peri-menopausal women	C allele or TC/CC genotypes linked to increased MetS risk and obesity markers in 5 of 10 studies. Association stronger when estradiol levels are low, suggesting gene-hormone interaction.
ESR2	rs3020449	Polish, Mongolian, US	Strong association with MetS and unfavorable lipids in Polish cohort; no association in Mongolian and US studies.
ESR2	rs1256049 (RsaI) & rs4986938 (AluI)	Mainly Chinese and mixed	Mixed results: minor alleles linked to adverse lipid profiles in two Chinese studies; majority of other studies report no significant association.

DISCUSSION

Biological Plausibility

Estrogen receptors are a significant factor in realizing the effects of estrogen on metabolic regulation. This passage will discuss how variations of genes, ESR1 and ESR2, might significantly regulation this pathway. Estrogen Receptor alpha (ERα), known from the ESR1 gene, is the lead estrogen receptor usually found in the major metabolic tissues that are the sites for liver, adipose tissue, and skeletal muscle. A specific variant in intron 1 of the ESR1 gene (rs2234693 (PvuII) and rs9340799 (XbaI)) have been shown to notably influence enhancer activity and hence receptor availability at the cellular level. This kind of reaction may result in gene transcription involved in cholesterol metabolism, insulin signaling, and blood sugar level homeostasis. Experimental investigations prove that when the activity of ERα is decreased, insulin sensitivity is reduced, and the intra-abdominal fat gets accumulated, which makes one be more prone to the features of the metabolic syndrome (Schroth *et al*., 2010).

Preceding mainly tissue-specific expression and, at the same time, potential furthers ERβ, the ESR2 gene, is quite a well-researched area. In different situations, it has the ability to change the effects of ERα if they become excessive. Thus, changes in the ESR2 gene (i.e. promoter polymorphisms) have the possibility to regulate the level and timing of receptor expression in metabolic tissues. However, direct links established between ESR2 variants and metabolic syndrome are not so strong and have low consistency, which may be due to the small size of the effect or differences from one population to another (Schroth *et al*., 2010). On the whole, even though mechanistic exploring proposes that both receptors take part in the metabolic regulation, the great majority of genetic association studies underline clearly ESR1's dominant role, particularly during estrogen decline in menopause transition (Goulart *et al*., 2009).

Heterogeneity Drivers

One of the chief reasons for the variability in clinical studies when examining ESR1 and ESR2 polymorphisms and metabolic syndrome is that the studies mainly spring from different sources of heterogeneity (Ghal *et al*., 2018).

One of the major sources of variability is the ethnic differences in the allele frequencies of critical polymorphisms like rs9340799 has been known for a long time (Krakowiak *et al*., 2022). Given that the presence of the G allele varies from about 0.18 in some Asian cohorts to the same is 0.56 in some of the European populations and this frequency is a very big difference (Bai *et al*., 2018). These different frequencies not only obviously affect the statistics of the association of certain genotypes and the predictions of possible causal variants of linkage disequilibrium but also disturb allelic diversity through the population (Zhou *et al*., 2018). Thus, if certain associations exist in one population, there is no guarantee that those results would be the same in the other population (Kuźbicka *et al*., 2012).

Additionally, the amount of estrogen in the blood and the menopause stage act as crucial contributors to the genetic risk. Correspondingly, as estrogen is produced in lower quantities due to the onset of menopause, the genetic β-phenotype link of the estrogen receptor gene may become more marked. As a consequence of several studies that stipulate the ESR1 polymorphisms and metabolic syndrome as well as with its components also present a clearer link only during those stages

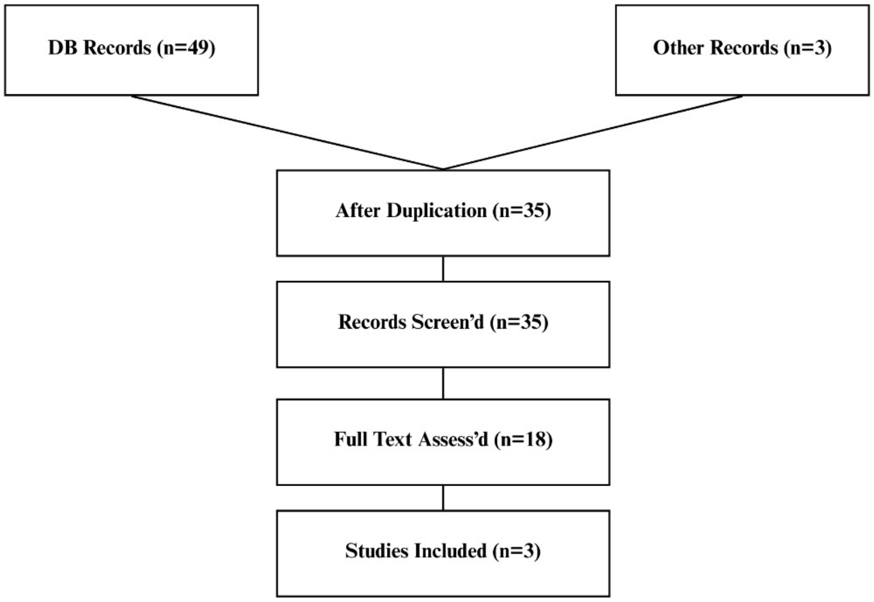

Figure 1: PRISMA flow diagram of study selection.

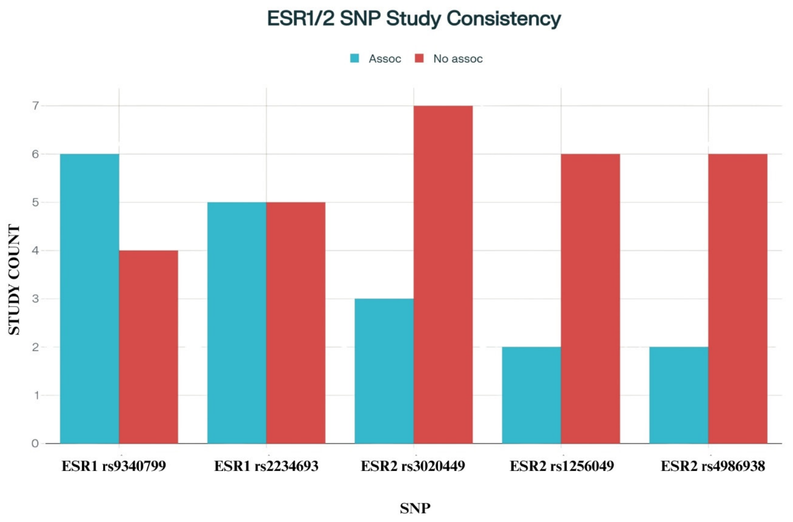

Figure 2: Evidence consistency for key SNPs.

of the menopausal period, it is cogent to note that there might be a dynamic process that is in play between the dwindling levels of estrogen and the genetic predilection that women undertake as they go through the menopausal-all that begets the shift (Goulart *et al.*, 2009).

The latest research suggests that the effect of genetic risk is more evident when BMI and fat levels interact. The analyses performed with a classification of BMI have been comprehended as the leading way to tackle the issue of how both genes, ESR1, and ESR2, predominantly the first, responded to the effect of overweight and obesity in women. It is found that, whereas the impact of women's obesity on the genotypic expression of ESR1 and ESR2 is certain, it is a conclusion that is subject to debate in the case of ESR2 (Bai *et al.*, 2013). The reason for this can be traced to the fact that fatness stands as one of the causes of the systemic inflammatory state, the insulin resistance state or the estrogen metabolism which will damage this hormone, and those other reactions cause the genotype to be more visible on the phenotype. The studies referred to in the analysis, among other things, have shown that the genetic effects were significantly in people with a high BMI, which emphasizes the role of these factors in the direction of the risk and genetic constitutive effects (Ahmed *et al.*, 2022).

The pathway to reach metabolic syndrome in menopausal women through the involvement of ESR1 and ESR2 genetic variants is characterized by a series of intersections between the genetic, hormonal, and environmental realms. As a result, a clear understanding of these intersections will be crucial when it comes to employing genetic findings as means of providing accurate risk estimates and implementing interventions targeted at metabolic health issues during menopause.

CONCLUSION

The evidence synthesized in this systematic review indicates that polymorphisms in the ESR1 gene, particularly the intronic variants rs9340799 (XbaI) and rs2234693 (PvuII), are moderately associated with increased susceptibility to metabolic syndrome and its components-such as obesity, dyslipidemia, and insulin resistance in menopausal women. The influence of ESR2 gene variants appears less consistent and more population specific. These genetic effects are further modulated by gene-environment interactions involving body mass index, ethnicity, and circulating estradiol levels, highlighting a complex interplay between inherited factors and hormonal changes characteristic of the menopausal transition. Overall, this review underscores the clinical relevance of estrogen receptor gene polymorphisms as contributors to cardiometabolic risk in menopausal women and supports the potential for integrating genetic profiling into personalized prevention and management strategies for metabolic syndrome in this vulnerable population.

ABBREVIATIONS

ESR1: Estrogen Receptor Alpha Gene; **ESR2:** Estrogen Receptor Beta Gene; **MetS:** Metabolic Syndrome; **ERα:** Estrogen Receptor Alpha; **ERβ:** Estrogen Receptor Beta; **SNPs:** Single-Nucleotide Polymorphisms; **SNP:** Single-Nucleotide Polymorphism; **HRT:** Hormone Replacement Therapy; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **MeSH:** Medical Subject Headings; **NCEP-ATP III:** National Cholesterol Education Program – Adult Treatment Panel III; **IDF:** International Diabetes Federation; **mRNA:** Messenger Ribonucleic Acid; **GWAS:** Genome-Wide Association Study; **SAT:** Subcutaneous Adipose Tissue; **VAT:** Visceral Adipose Tissue; **HOMA-IR:** Homeostatic Model Assessment of Insulin Resistance; **BMI:** Body Mass Index; **HDL-C:** High-Density

Lipoprotein Cholesterol; **LDL:** Low-Density Lipoprotein; **LDL-C:** Low-Density Lipoprotein Cholesterol; **E2:** Estradiol.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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