Maturitas 166 (2022) 65–85

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Practice Guidelines

Eligibility criteria for Menopausal Hormone Therapy (MHT): a position statement from a consortium of scientific societies for the use of MHT in women with medical conditions. MHT Eligibility Criteria Group

ARTICLE INFO

Keywords
Menopausal hormone therapy
Menopause
Eligibility criteria
Medical conditions

ABSTRACT

This project aims to develop eligibility criteria for menopausal hormone therapy (MHT). The tool should be similar to those already established for contraception A consortium of scientific societies coordinated by the Spanish Menopause Society met to formulate recommendations for the use of MHT by women with medical conditions based on the best available evidence. The project was developed in two phases. As a first step, we conducted 14 systematic reviews and 32 metanalyses on the safety of MHT (in nine areas: age, time of menopause onset, treatment duration, women with thrombotic risk, women with a personal history of cardiovascular disease, women with metabolic syndrome, women with gastrointestinal diseases, survivors of breast cancer or of other cancers, and women who smoke) and on the most relevant pharmacological interactions with MHT. These systematic reviews and metanalyses helped inform a structured process in which a panel of experts defined the eligibility criteria according to a specific framework, which facilitated the discussion and development process. To unify the proposal, the following eligibility criteria have been defined in accordance with the WHO international nomenclature for the different alternatives for MHT (category 1, no restriction on the use of MHT; category 2, the benefits outweigh the risks; category 3, the risks generally outweigh the benefits; category 4, MHT should not be used). Quality was classified as high, moderate, low or very low, based on several factors (including risk of bias, inaccuracy, inconsistency, lack of directionality and publication bias). When no direct evidence was identified, but plausibility, clinical experience or indirect evidence were available, "Expert opinion" was categorized. For the first time, a set of eligibility criteria, based on clinical evidence and developed according to the most rigorous methodological tools, has been defined. This will provide health professionals with a powerful decision-making tool that can be used to manage menopausal symptoms.

1. Introduction

The data collected during the last two decades on the effects of menopausal hormone therapy (MHT) could help to provide a safer and more effective treatment of menopause symptoms as well as an improved quality of life [1–2]. Based on all of this information, international societies have concluded that the benefits of MHT outweigh the risks in healthy symptomatic postmenopausal women when MHT is initiated within 10 years of the menopause or when younger than 60 years of age [3,4].

However, there are currently no guidelines available that provide specific recommendations on the prescription of MHT in postmenopausal women with any medical condition. In the absence of reliable information, the fear of aggravation of the pre-existing condition prevents the general practitioner or health care provider from prescribing MHT when symptoms impair quality of life.

In the case of contraceptive methods, there is a globally available document that provides information for this purpose. Thus, the "WHO Medical Eligibility Criteria" classifies the various medical conditions of women into four categories, providing the scientific community with recommendations for the safe use of any contraceptive method [5].

The objective of this study was to create eligibility criteria for the use of MHT similar to those established for contraceptive methods. A consortium of Scientific Societies coordinated by the Spanish Menopause Society (Asociación Española para el Estudio de la Menopausia, AEEM, see Appendix 1) met to define eligibility criteria for the use of THM in women with main medical conditions found in the researched database.

2. Methodology

The study was conducted in two phases. As a first step, we conducted a series of systematic reviews on the safety of MHT, addressing nine clinical questions. We then developed a working framework to formulate explicit, reasoned recommendations. The findings of these systematic reviews helped to inform a structured process in which a panel of experts defined the eligibility criteria according to a specific framework, which facilitated the discussion and development process.

The objectives and methodology (Systematic reviews for the definition of MHT eligibility criteria) are described in a previous paper [6].

https://doi.org/10.1016/j.maturitas.2022.08.008
Received 16 March 2022; Received in revised form 21 June 2022; Accepted 17 August 2022
Available online 30 August 2022

2.1. Evidence synthesis

2.1.1. Definition of clinical questions

We defined a common protocol for conducting a systematic review to respond to eight clinical questions concerning various conditions. The protocol was registered in PROSPERO (registration number CRD42020166658) and in the Open Science Framework platform (DOI 10.17605/OSF.IO/J6WBC). The reviews were conducted according to standardised criteria [7]. First, members from the expert panel defined the specific clinical questions:

- How safe is MHT according to age, time of menopause onset, and treatment duration?
- How safe is MHT in women with thrombotic risk?
- How safe is MHT in women with a personal history of cardiovascular disease?
- How safe is MHT in women with metabolic syndrome?
- How safe is MHT in women with gastrointestinal diseases?
- How safe is MHT in female survivors of breast cancer?
- How safe is MHT in female survivors of other cancers?
- How safe is MHT in smoking women?
- Which are the most important pharmacological interactions with MHT?

More specifically, these questions focused on the age of the women, the time after menopause at which MHT is prescribed and its duration, along with the risks associated with previous cancers and comorbidities such as endocrine, digestive and cardiovascular diseases.

We additionally explored the impact of hypertension, obesity, migraines, smoking and prothrombotic mutations as additional risk factors to the conditions defined through the clinical questions. Finally, we considered the most common drugs that interact with MHT. The members of the panel — with the support of two experts in evidence synthesis methodology — framed the clinical questions to define the population and sub-groups of interest and to identify the outcomes of interest [8], establishing the inclusion criteria for the systematic reviews.

2.1.2. Inclusion criteria

The systematic reviews included randomized controlled trials, and related extension studies or follow-up reports. Additionally, we included observational studies (with special interest in population-based cohorts or large case-control studies), including a control group of non-users. Studies considered eligible if they included menopausal women of any age receiving MHT, and affected by any of the conditions of interest defined in the clinical questions.

We considered studies that evaluate any MHT regimen (oestrogens alone in hysterectomized women or combined with a progestogen, tibolone or tissue-selective oestrogen complex) with any route of administration (oral, transdermal, vaginal or intra-nasal). The impact of MHT was compared with placebo or non-treatment controls. We defined a range of specific clinical outcomes of interest according to the scope of each clinical question (e.g., recurrence of disease for cancer survivors or new thromboembolic events in women with cardiovascular or thrombotic risk).

2.1.3. Searches and eligibility

We conducted exhaustive literature searches in the following databases: MEDLINE (via PubMed), The Cochrane Library (CENTRAL), and EMBASE (via embase.com), from their inception until the most recent date. We designed a search strategy that is tailored to the requirements of each database, which included a combination of controlled vocabulary and search terms related to each clinical question and the associated inclusion criteria. Appendix 2 displays an exploratory search strategy for MEDLINE. When necessary, we used validated filters to retrieve the appropriate study designs.

Additionally, we checked the reference lists of relevant studies or reviews identified and map any secondary publications from large studies in the field (e.g., the Women's health initiative trial for most of the clinical questions or the Estrogen in Venous Thromboembolism Trial to assess safety in women with a history of thromboembolic disease). Initially, no restrictions were applied in terms of language, date, or status of publication.

Two independent researchers screened the references yielded by the search to reach an agreement on the inclusion of studies for each review, according to the criteria defined for each clinical question. We involved a member of the expert panel to resolve any discrepancies. The panel members were informed about this process in order to evaluate the suitability of the included studies and suggested additional studies if relevant articles were omitted.

2.1.4. Data extraction and risk of bias assessment

The Panel, which comprised the authors of the study, reviewed the scientific literature according to a protocol following methodological guidelines from the Cochrane collaboration [7] and reported its findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8]. For observational studies, we adapted the ROBINS I tool, focusing on the evaluation of the impact of the confounding variables, selection bias, outcome measures, and attrition [9].

We made explicit judgements on the certainty of the evidence for each outcome of interest according to GRADE criteria [10]. Quality was classified as high (A), moderate (B), low (C) or very low (D), based on several factors (including risk of bias, inaccuracy, inconsistency, lack of directionality and publication bias). In those systematic reviews where no direct evidence was identified, but plausibility was considered to exist or clinical experience or publications with indirect evidence were available, consensus decisions were made by the panel and categorised as "Expert opinion".

2.1.5. Data synthesis

We described the synthesis of the evidence for each clinical question in reports that followed the PRISMA guidelines. We developed a narrative synthesis of the findings and effect estimates from the included studies focusing on the outcomes of interest, to explore the association between the MHT and the outcomes of interest.

When appropriated, pooled analyses were conducted using the Mantel-Haenszel method and the random effects model included within the RevMan software statistical package (v 5.3.5) [11].

We reported explicit judgments to rate the quality of the evidence for each outcome. The results and quality assessment of each outcome of interest were presented in the summary of findings tables [10–12].

2.2. Evidence to decision framework and eligibility criteria

In order to formulate the recommendations in an explicit and reasoned manner, we used an evidence to decision (EtD) framework to inform the Panel of the most relevant aspects necessary for taking decisions and thus making them easy to justify [13].

To produce a ranking of MHT eligibility criteria, The Panel integrated the findings of the reviews according to a structured framework that considered the magnitude of the MHT effects for each outcome and population of interest, the certainty ratings of the evidence, and data from other sources of evidence.

To unify the proposal, the following eligibility criteria have been defined in accordance with the WHO international nomenclature:

- Category 1: No restriction on the use of MHT
- Category 2: The benefits outweigh the risks.
- Category 3: The risks generally outweigh the benefits.
- Category 4: MHT Should not be used

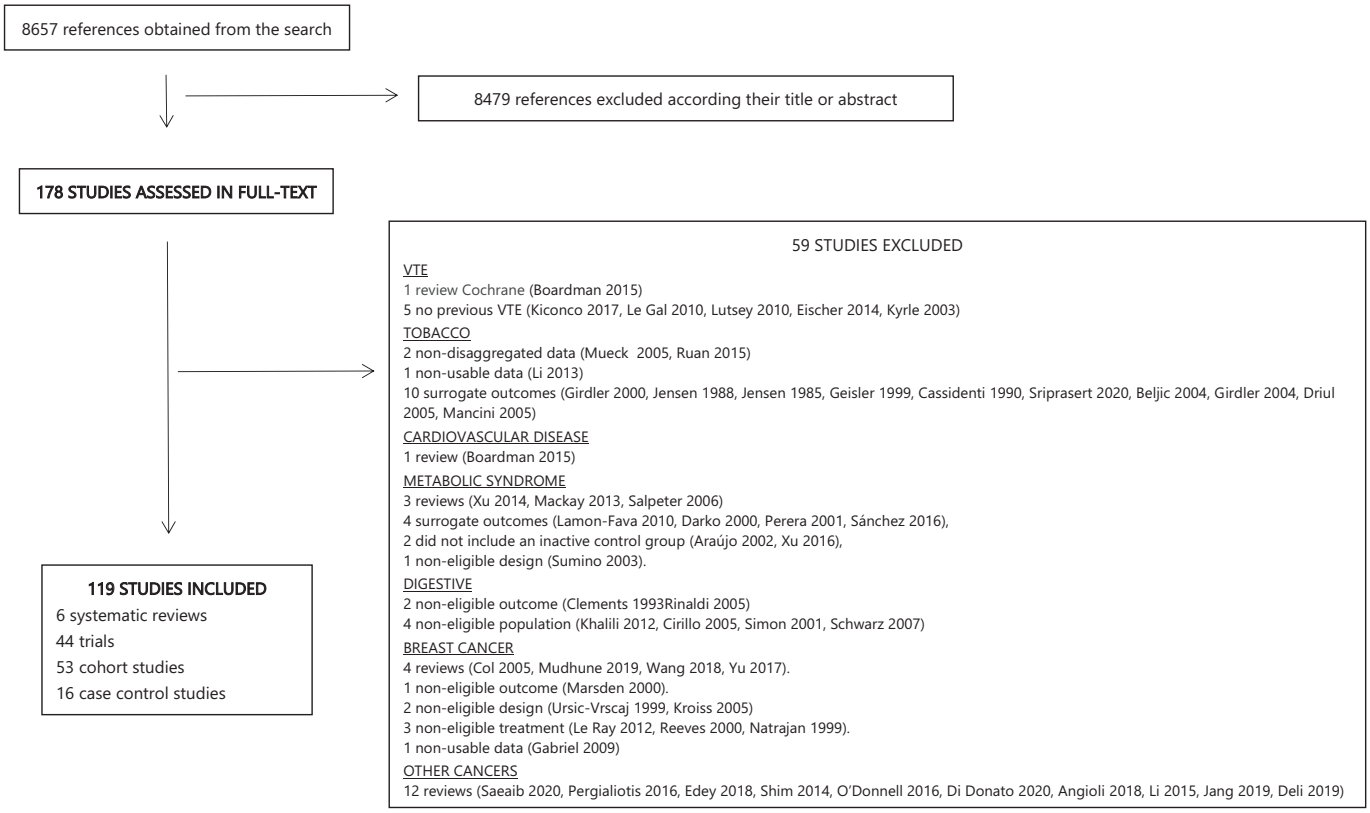

Fig. 1. PRISMA flowchart for the clinical questions defined by the MHT Eligibility Criteria Group

Table 1
Age, duration and MHT eligibility criteria

Condition		Combined MHT		Oestrogens-only MHT		Tibolone	Local MHT[1]	Clarifications
Age	Duration	Oral	Trsd	Oral	Trsd			
<40[2],*	<5 years	1C	1	1C	1C	NA	1	* For tibolone, the available evidence is for safety with respect to the risk of VT/PE and breast cancer (>50 years). There is no evidence for cardiovascular risk.
	≥5 years	1C	1C	1C	1C	NA	1	
40–44[3],*	<5 years	2C	1C	2C	1C	2C**	1	
	≥5 years	2C	2C	2C	2C	2C**	1	** The available evidence is low due to the limited number of cases included in the studies. The clear benefit of using MHT in women under 50 years of age should be considered.
45–49[3],*	<5 years	2C	2C	2C	1C	2C**	1	
	≥5 years	2C	2C	2C	2C	2C**	1	
50–59	<5 years	2B	2B	2B	2B	2C (<55) 1C (>55)	1	*** MHT Continuation (Category 2)/MHT initiation >10 years after menopause (Category 3)
	≥5 years	2B	2B	2B	2B	2C (<55) 1C (>55)	1	
60–69	<5 years	2/ 3B***	2/ 3B***	2/ 3B***	2/ 3B***	2C	1	
	≥5 years	2/ 3***	2/ 3***	2/ 3***	2/ 3***	2C	1	
>70	<5 years	3D	3D	3D	3D	2C	1	
	≥5 years	3D	3D	3D	3D	3C	1	

MHT: menopausal hormonal therapy; NA = not applicable due to lack of available evidence; Trsd = transdermal; VT/PE: venous thrombosis/pulmonary embolism

[1] For easy to understand, no quality studies address the local administration of estrogens and the co-morbidities analyzed. Thus, expert opinion has rated these situations based on biological plausibility and clinical experience

[2] The group of menopauses under 40 is defined now by the term premature ovarian insufficiency (POI). Guidelines suggest that MHT should be continued until the average age of menopause (age 50–51 years) to prevent premature bone loss, coronary heart disease, stroke, and an increased risk of dementia. At that point, if MHT is stopped and menopausal symptoms are moderate to severe, the same discussion of potential risks and benefits of MHT should take place.

[3] If hormonal contraception is needed, it is recommended to maintain it until age 50.

2.3. Exceptional situations

The term MHT embraces a wide variety of preparations (synthetic and natural) used with different compositions, routes of administration, and dosage. This heterogeneity implies different effects of the interaction with the medical conditions analysed. The wide range of combinations adds variability to drug interactions or medical conditions. For this reason, we mentioned the peculiarities regarding routes or doses within each section. Moreover, in some therapeutic groups, the eligibility assignment may include more than one number due to differences, explained in the footnote. We have explicitly analysed some treatment regimens targeting steroid receptors and not being ovarian steroids.

The TSEC complex is a drug combination of oestrogen and selective in the SERM group since it is associated with MHT.

Tibolone, despite being a progestogen as a molecule, has its own column due to its particular characteristics, clinical effects comparable to combined MHT, and evidence of influence on medical conditions and possible interactions has its specific molecule.

Quality evidence on the effects of vaginal MHT is scarce. Pharmacodynamic studies show a lack of absorption and systemic effects after two weeks of use. Clinical experience supports the absence of effects or drug-drug interactions and influences on medical conditions.

Beyond this article, the reports of the groups analysing the evidence gathered for each question will be published in a complete document and, when appropriated, in specific papers.

3. Results

3.1. Systematic reviews and meta-analyses

After the first search, we identified 8657 articles fulfilling the search strategy terms. Among them, we selected 236 studies which were prospective, peer-reviewed and had at least one arm of MHT [14–249] (see Fig. 1 and Appendix 3).

A total of 14 systematic reviews were conducted (three for age, three for thrombosis, two for CVD, one for digestive issues, one for metabolic syndrome, two for breast cancer, one for other cancers, and one for tobacco). Moreover, a specific one reviews reference to address the

Table 2
Medical conditions and MHT eligibility criteria

Condition		Combined MHT		Oestrogens-only MHT		Tibolone	Local MHT[a]	Clarifications
		Oral	Trsd	Oral	Trsd			
Thrombotic risk	VT/PE without anticoagulation	4B	3C	4B	3C	NA	1	
	VT/PE with anticoagulation		3D*		3D*			* If necessary, the transdermal MHT is preferred (expert opinion).
	Asymptomatic thrombophilia	4B	2B	3B	2B	NA	1	
Neurological disorders	Migraine Without aura	2C*	2	2	2	NA	1	Continuous administration of MHT can avoid the estrogen withdrawal migraine
	With aura	3D*	2C (O)/ 3C* (C)	3D*	2C (O)/ 3C* (C)	2C (O)/ 3C*(C)	1	* The administration of an antiplatelet agent may be considered (expert opinion). O (Onset): Migraine occurs before MHT). C (continuation): migraine occurs after MHT).
	Tension headache	1B	1B	NA	NA	1	1	
Cardiovascular disease	Stroke	3A	3A/ D2*	3A	3A/2D*	NA	1	*Exception: young women whose stroke is not due to arteriosclerosis, or after haemorrhagic strokes with a normal coronary history and without other associated RF (diabetes mellitus, smoking, hypertension or dyslipidaemia). Expert opinion.
	Non-fatal AMI	3A/ 2D*	3A/ 2D*	3A/ 2C**	3A/ 2C***	NA	1	* No ischaemic cause of AMI or other RF (Expert opinion). ** Those who have undergone coronary artery bypass grafting with saphenous vein grafting have a better prognosis if they are under MHT with oestrogen alone at the time of revascularisation. Therefore, in these patients it could be recommended to maintain MHT.
	Angina	2A/ 3D*	2A/ 3D*	2A/ 3D+	2A/3D*	NA	1	*ischaemic cause or with other RFs (Expert opinion).
	High blood pressure	2B/ 1A***	2B	2B/ 1B****	2B	2B	1	*** Combination of oestradiol + drospirenone. **** Combination of oestradiol + noretisterone.
Smoking		3C	2C	3C	2C	NA	1	
Metabolic disorders related to the metabolic syndrome	Diabetes mellitus	1B	1D	2C	1D	NA	1	
	Hypercholesterolemia	1D	1D	1D	1D	NA	1	
	Hypercholesterolemia and diabetes	1C	1C	1C	1C	NA	1	
	BMI 25-30 kg/m2	2B	1B	2B	1B	NA	1	
	BMI >30 kg/m2*	3B	2B	3B	2B	NA	1	* No data in women with BMI>35.
Digestive Diseases	Inflammatory bowel disease*	2D	1D	2D	1D	NA	1	* Assess additional thrombotic risk factors.
	History of hepatitis C	2C	2C	2C	2C	NA	1	
	Acute hepatitis	4/ 3D**	4/ 3D**	4/2D**	4/2D**	NA	1	**Depending on the severity of the condition.
	Cirrhosis	NA*	NA*	NA*	NA*	NA*	1	* Not because of the preparation but because of liver damage. Category 4 would apply (expert opinion).

AMI = acute myocardial infarction; BMI = body mass index; BP = blood pressure; HC = hormonal contraceptives; MHT: menopausal hormonal therapy; NA = not applicable due to lack of available evidence; RF = risk factor; Trsd = transdermal; VT/PE: venous thrombosis/pulmonary embolism

[a] For easy to understand, no quality studies address the local administration of estrogens and the co-morbidities analyzed. Thus, expert opinion has rated these situations based on biological plausibility and clinical experience.

question of drug interactions.

In addition, 32 meta-analyses were conducted: seven for CVD, three for metabolic syndrome, nine for breast cancer, and thirteen for other cancers.

3.2. MHT eligibility criteria

In Tables 1 to 4, we present the recommendations of the different analysis groups after being reviewed by internal and external committees.

They show the results of analysing 252 potential scenarios combining clinical conditions and MHT alternatives. We have identified 8(3,2%) combinations rated with a 4. The group considered that the prescription of any of the forms of MHT should be avoided.

In 28 scenarios (11,1%), the evaluating group considered that the risks outweighed the benefits and rated the situation 3. Furthermore, in 21 potential clinical situations (8,3%), the rating is between 2 and 3 according to specified circumstances.

Consequently, MHT has been safe or with the benefits being higher than the potential threats (rated 1 or 2) in 164 potential combinations (65.1%).

4. Discussion

The objective of this project was to create a set of eligibility criteria for the use of MHT, similar to those established for contraceptive methods. A consortium of scientific societies coordinated by AEEM met to develop a set of guidelines on the use of MHT in women depending on age and duration of use or with various medical conditions based on the best available evidence.

MHT is underused according to the difference between the published incidence of severe symptoms and the estimated number of users. A relevant driver for this underuse is the fear from both women and prescribers of inducing more harm than benefit. Excessive precaution is even more critical when dealing with women presenting additional morbidities. Moreover, quality evidence exploring the effects of MHT on pathological situations is scarce. To our knowledge, a tool that assists clinicians in the decision-making process of MHT prescribing in these situations is unavailable [250–252].

A group of experienced clinicians selected by the Spanish Menopause Society (AEEM) have identified nine frequent clinical scenarios that could make the counselling process difficult. After analysing the evidence available for any scenario combined with any MHT type, we have identified 36 out of 252 (14,3%) combinations where these treatments should be avoided. A systematic review identified 236 papers contributing to understanding the potential effects of any MHT in these patients.

These findings suggest a treatment alternative for severely symptomatic women where the benefits outweigh the risks in most clinical scenarios. With this information, health care providers counselling postmenopausal women will have a readily available tool to identify potentially risky situations. Consequently, the number of women accessing a needed MHT should increase.

The most critical limitation found during the development of the tool has been the limited number of quality studies exploring specifically the interaction between diseases or situations and MHT alternatives. No studies address specific clinical conditions for some approaches (route, presentation or molecule) and vice versa. In some of these cases, the final decision has been taken based on the best available evidence that was, unfortunately, expert opinion based on the data obtained in healthy women.

A relevant strength of the tool is the quality of the review process by identifying studies, evaluating their quality, and the degree of recommendation that could be drawn from them. Throughout the process, a rigorous and systematic methodology has been applied in accordance with internationally accepted guidelines. The quality of the tool is enhanced by the wide external and internal reviews. The process involved up to 21 members of Spanish and international scientific societies related to the diseases explored in the study. Their comments and recommendations have been either discussed or included in the tool.

We hope that a widespread diffusion of this decision tool will increase the use of MHT in severely symptomatic postmenopausal women affected by frequent comorbidities. The tool has to be updated as new non-analysed scenarios are identified.

Our report has undoubtedly identified some important areas for improvement for future research. We expect that our findings will contribute to the development of studies that continue to analyse the safety and efficacy of MHT in treating menopausal symptoms in women with the medical conditions described. More extensive RCTs should be conducted, and over a longer follow-up period, to evaluate the various MHT strategies.

Table 3
Cancer and MHT eligibility criteria

Condition		Combined MHT		Oestrogens-only MHT		Tibolone	Local MHT	Clarifications
		Oral	Trsd	Oral	Trsd			
Breast cancer	BCS (HR-)	2B	2B	2B	2B	2B	2D*	* Recommendation based on the opinion of regulatory agencies.
	BCS (HR+)	3C	3C	3C	3C	4A	2D*	* Recommendation based on the opinion of regulatory agencies.
	BRCA carrier1	2C	2C	2C	2C	NA	1D	
	BRCA2 carrier*	2D*	2D*	2D*	2D*	NA	1D	* BRCA1 extrapolation (expert opinion).
Gynaecological cancers	Ovarian cancer	1B*	1B*	1B*	1B*	1B*	1D	* Longer survival and lower recurrence, particularly in those under 55 years of age. There does not appear to be a difference according to type of MHT or route of administration. There is no literature that supports or excludes MHT for non-epithelial tumours.
	Endometrial cancer	2C*	2C*	2C*	2C*	2C*	1D	* No differences in DFS (less recurrence with combined MHT than with oestrogen-only MHT).
	Cervical cancer	2C*	2C*	2C*	2C*	2C*	1D	*No difference in survival or DFS. Little evidence.
Other cancers	Colon cancer	1C*	1C*	1C*	1C*	NA	1D	* No differences between different forms of MHT are evaluated. ** Seems to show better results with oestrogens-only MHT.
	Lung cancer	2C*	2C*	2C*	2C*	NA	1D	* No differences between different forms of MHT are assessed. Smoking increases the risk.
	Melanoma	2C*	2C*	2C*	2C*	NA	1D	* Only one cohort study with a large 10-year follow-up.

BCS = Breast cancer survivors; DFS = disease-free survival; HR = hormonal receptors; MHT: menopausal hormonal therapy; NA = not applicable due to lack of available evidence; RF = risk factor; Trsd = transdermal.

Table 4
Drug interactions and MHT eligibility criteria[a].

Drug	Combined MHT		Oestrogens-only MHT		Tibolone	Local MHT	Clarifications
	Oral	Trsd	Oral	Trsd			
Antihypertensives*	1**/ 2***	1	2***	1	2***	1	* Despite the lack of possible interaction studies, the evidence of extensive co-use without reporting associated problems is considered sufficiently relevant. **With drospirenone. *** In some patients, probably with certain idiosyncrasies, oral MHT may alter BP control and require dose adjustment and confirmation that this is resolved.
Statins*	1/2**	1 ***	1/ 2**	1 ***	1/2**	1	*same comment as with antihypertensives. ** Oral MHT tends to increase triglycerides, total cholesterol and LDL-cholesterol, and to increase HDL-cholesterol. No interaction, but consider according to patient profile. *** Transdermal MHT modifies lipid profile less. No interaction but consider if there is indication or loss of desirable benefit according to patient profile.
Anxiolytic/hypnotics	1	1	1	1	1/2*	1	* Midazolan.
Analgesics/anti-inflammatories	1	1	1	1	1	1	
Antidepressants	1	1	1	1	1	1	
Aromatase inhibitors	4	4	4	4	4	1	
Oral anti-diabetics	1	1	1	1	1	1	
Insulin	1	1	1	1	1	1	
Thyroid hormones*	1	1	1	1	1	1	* Assess dose adjustment (little clinical relevance)
Bronchodilators	1*	1	1*	1	1*	1	* With oral theophylline adjust dose.
Anticoagulants	1/2*	1	1/2*	1	2*	1	* In some women (particularly at baseline), adjustment of the warfarin anticoagulant dose, discontinuation of MHT, or change of administration route may be required
SERMS	4	4	4	4	4		
Corticoids	2	2	2	2	2	1	
Antiepileptics *	4	3	4	3	4	1	* Most antiepileptic drugs are potent enzyme inducers, and could thus reduce oestrogenic effectiveness. Oral MHT may reduce the effect of the antiepileptic drug by interfering with its metabolism.
Enzyme inhibitor antibiotics (rifampicin/rifbutin)	2	2	2	2	2	1	
Antineoplastics	4	4	4	4	4	1	
Immunosuppressors	3	3	3	3	3	1	
Oral antifungals	1/2*	1	1/2*	1	1/2*	1	*In chronic treatments.
Antiretrovirals	1/2*	1/ 2*	1/2*	1/ 2*	1/2*	1	Tipranavir) are enzyme inducers and reduce the oestrogenic effect; but non-nucleoside reverse transcriptase inhibitors (Efavirenz, Nivirapine) are enzyme inducers that do not reduce the oestrogenic effect.
Dopaminergics	2	2	2	2	2	1	In the rare cases where these substances have to be administered in postmenopausal women with prolactinoma, MHT does not interfere with the tumour control effect.
Litolitics*	3	2	3	2	3	1	* Decreased litholytic effect and increased hepatic cholesterol have been reported with HC, which could perhaps occur with oral MHT.
Neurostimulants	2	2	2	2	2	1	
Antithyroid	2	2	2	2	2	1	
Antipsychotics *	2/3*	2/ 3*	1	1	1	1	* Some studies have reported progestogen interaction for aripiprazole and pimozide.

HC = hormonal contraceptives; MHT: menopausal hormonal therapy; NA = not applicable due to lack of available evidence; RF = risk factor; Trsd = transdermal; SERM: selective estrogen receptor modulators

[a] For easy to understand, no quality studies address the interactions between unfrequent medications and MHT. Similarly happens with the local administration of estrogens and the co-morbidities analyzed. Thus, expert opinion has rated these situations based on biological plausibility and clinical experience.

Contributors

Nicolás Mendoza contributed to conception and design of the idea, coordination and preparation of manuscript, manuscript editing, and was a member of the Expert Panel.

Isabel Ramírez contributed to conception and design of the idea, coordination and preparation of manuscript, and was a member of the Expert Panel.

Esther de la Viuda contributed to conception and design of the idea, coordination and preparation of manuscript, and was a member of the Expert Panel.

Pluvio Coronado coordination and preparation of manuscript.

Laura Baquedano coordination and preparation of manuscript, and was a member of the Expert Panel.

Plácido Llaneza coordination and preparation of manuscript, and was a member of the Expert Panel.

Verónica Nieto coordination and preparation of manuscript.

Borja Otero coordination and preparation of manuscript, and was a member of the Expert Panel.

Sonia Sánchez-Méndez coordination and preparation of manuscript, and was a member of the Expert Panel.

Visitación Álvarez de Frutos was a member of the Expert Panel.

Leire Andraca was a member of the Expert Panel.

Patricio Barriga contributed to external review.

Zully Benítez contributed to external review.

Teresa Bombas contributed to external review.

Mª Jesús Cancelo contributed to external review.

Antonio Cano contributed to external review.

Camil Castelo Branco was a member of the Expert Panel.

Marta Correa was a member of the Expert Panel.

José Luis Doval was a member of the Expert Panel.

María Fasero was a member of the Expert Panel.

Gabriel Fiol was a member of the Expert Panel.

Nestor C Garello contributed to external review.

Andrea R Genazzani contributed to external review.

Ana Isabel Gómez was a member of the Expert Panel.

Mª Ángeles Gómez was a member of the Expert Panel.

Silvia González was a member of the Expert Panel.

Dimitrios G Goulis contributed to external review.
Misericordia Guinot was a member of the Expert Panel.
Luis Rolando Hernández contributed to external review.
Sonia Herrero was a member of the Expert Panel.
Eva Iglesias was a member of the Expert Panel.
Ana Rosa Jurado was a member of the Expert Panel and contributed to external review.
Iñaki Lete was a member of the Expert Panel.
Daniel Lubián was a member of the Expert Panel.
Milagros Martínez was a member of the Expert Panel.
Aníbal Nieto was a member of the Expert Panel.
Laura Nieto was a member of the Expert Panel.
Santiago Palacios contributed to external review.
Milagros Pedreira was a member of the Expert Panel.
Ezequiel Pérez-Campos was a member of the Expert Panel.
María Jesús Plá was a member of the Expert Panel.
Jesús Presa was a member of the Expert Panel.
Francisco Quereda was a member of the Expert Panel.
Miriam Ribes was a member of the Expert Panel.
Pablo Romero was a member of the Expert Panel.
Beatriz Roca was a member of the Expert Panel.
Antonio Sánchez-Capilla was a member of the Expert Panel.
Rafael Sánchez-Borrego contributed to external review.
Ana Santaballa was a member of the Expert Panel.
Amparo Santamaría was a member of the Expert Panel.
Tommaso Simoncini contributed to external review.
Francisco Tinahones was a member of the Expert Panel.
Joaquín Calaf contributed to conception and design of the idea, coordination and preparation of manuscript, manuscript editing, and was a member of the Expert Panel.
All authors participated in the preparation of the statement and approved the final version of the manuscript.

Funding

No funding was sought or received for the preparation of this position statement.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Declaration of competing interest

In the past 3 years the following have received grant support from:
Laura Baquedano: Organon, Theramex
Joaquín Calaf: None declared
Pluvio Coronado: MSD, Shionogi, Adventia, Procare, Abex
Esther De la Viuda: Adamed, Bayer, Exeltis, Effik, Gedeon Ritcher, MSD, Organon, Procare Health Iberia, Sandoz, Shionogi, Teva, Theramex
Plácido Llaneza: None declared
Nicolás Mendoza: Astellas Pharma, Shionogi
Verónica Nieto: None declared
Borja Otero: Exeltis Spain
Isabel María Ramírez: Exeltis, MSD, Pfizer
Sonia Sánchez: Gynea-Kern, Shionogi, Theramex, Organon, Isdin, Lacer, Uriach, Dermolab
Visitación Álvarez: None declared
Leire Andraca: None declared
Camil Castelo-Branco: Shionogi Europe
Marta Correa: None declared
José Luis Doval: Exeltis
María Fasero: MSD, Organon, Theramex, Shionoghi
Gabriel Fiol: MSD
Ana Isabel Gómez: None declared
María de los Ángeles Gómez: Theramex, Gedeon Richter y Exeltis
Silvia González: Isdin, MSD, Shionogi, Lacer
Misericordia Guinot: None declared
Sonia Herrero: None declared
Eva María Iglesias: Astellas Pharma, Shionoghi and Lacer
Ana Rosa Jurado: Astellas Pharma, Bayer, Stada, Exeltis, Shionogi, MSD
Iñaki Lete: Organon, Adamed España, Gedeon Ritcher
Daniel María Lubián: Shionogi, Exeltis and Adamed
Milagros Martínez: Shionoggi, Khern-Pharma
Aníbal Nieto: None declared
Laura Nieto: None declared
Milagros Pedreira: None declared
Ezequiel Pérez-Campos: Exeltis
María Jesús Plá: None declared
Jesús Presa: Theramex, Adamed Laboratorios, Kern Pharma
Francisco Quereda: Theramex, Shionoghi, Lacer, Gedeon Richter, Amgen, MSD
Miriam Ribes: Procareh
Beatriz Roca: Organon
Pablo Romero: None declared
Antonio Sánchez: None declared
Ana Santaballa: None declared
Amparo Santamaría: None declared
Iván Sola: None declared
Francisco Tahones: None declared
Zully Benítez: None declared
Teresa Bombas: None declared
María Jesús Cancelo: Shionogi Europe
Antonio Cano: Astellas, Theramex and Italfarmaco
Néstor C Garello: None declared
Andrea R Genazzani: None declared
Dimitrios G Goulis: None declared
Luis R Hernández: None declared
Santiago Palacios: Arkochim, Bayer Healthcare, Exeltis, Gedeon Richter, Novo Nordisk, Procare Health, Serelys, Mithra, Lacer, Sandoz
Rafael Sánchez Borrego: Seid SA, Lacer SA, Shionogi Slu, Exeltis, Astellas
Tommaso Simoncini: None declared

Acknowledgements

This article has been translated and edited by Your English Lab. Methodological support by Ivan Sola and Juan Carlos Vazquez, Biomedical Research Institute Sant Pau and CIBER Epidemiología y Salud Pública (CIBERESP).

Appendix 1. Consortium of scientific societies

Asociación Española para el Estudio de la Menopausia (AEEM)
European Menopause and Andropause Society (EMAS)
European Society of Gynecology (ESG)
Federación Latinoamericana de Sociedades de Obstetricia y Ginecología (FLASOG)

Federación Latinoamericana de Sociedades de Climaterio y Menopausia (FLASCYM)
Fundación Española para el Estudio de la Menopausia (FEEM)
International Menopause Society (IMS)
International Society of Gynecological Endocrinology (ISGE)
Red Iberoamericana de Salud Sexual y Reproductiva (REDISSER)
Sección de Ginecología Oncológica de la SEGO (SGOSEGO)
Sociedad Española de Cardiología (SEC)
Sociedad Española de Contracepción (SEC)
Sociedad Española de endocrinología y nutrición (SEEN)
Sociedad Española de Farmacia Comunitaria (SEFAC)
Sociedad Española de Ginecología y Obstetricia (SEGO)
Sociedad Española de Hematología y Hemoterapia (SEHH)
Sociedad Española de Médicos de Atención Primaria (SEMERGEN)
Sociedad Española de Oncología Médica (SEOM)
Sociedad Española de Patología Digestiva (SEPD)
Sociedad Española de Senología y Patología Mamaria (SESPM)
Sociedad Española de Trombosis y Hemostasia (SETH)
Sociedad Española para el Estudio de la Obesidad (SEEDO)

Appendix 2. Exploratory search designed for medline (accessed through PubMed)

("Hormone Replacement Therapy"[MeSH Major Topic] OR "hormone therapy"[Title] OR ("hormone*"[Title] AND "therapy"[Title] AND "menopause*"[Title]) OR "menopausal hormone therapy"[Title/Abstract] OR "Hormone Replacement Therapy"[Title/Abstract]

Appendix 3. Included studies by clinical question

Included studies by clinical question	
AGE	6 reviews or pooled data sets (CGHFBC 2019, CGESOC 2015, Nudy 2019, Kim 2020, Oliver-Williams 2019, Zhu 2019) 4 trials (Chlebowski 2010, Anderson 2012, Manson 2013, Manson 2017) 1 case control (Vinogradova 2020)
VTE	7 trials (Høibraaten 2001, Herrington 2002, Cushman 2004, EVTET 2000, Nappi 2001, Facchinetti 2002, Nappi 2006) 3 cohorts (Olié 2011, Rossouw 2002, Li 2015) 4 case control (Lowe 2000, Rosendaal 2002, Straczek 2005, Douketis 2010)
CARDIOVASCULAR DISEASE	9 trials (EAGAR 2006, ERA 2000, ESPRIT 2002, HERS I 1998, PHASE 2002, WAVE 2002, WELL-HART 2003, WEST 2001, WHISP 2006) 7 cohorts (Alexander 2001, Angeja 2001, Anveden 2015, Apostolakis 2014, Bretler 2012, Grodstein 2001, Khan 2000) 2 case control (Lindenfeld 2003, Nussmeier 2002)
TOBACCO	2 cohorts (Malek 2019, Wilson 1985) 1 case control (Mann 1994)
METABOLIC SYNDROME – DIGESTIVE DISEASES	16 trials (Mosnier–Pudar 1991, Brussaard 1997, Cornu 2000, Sutherland 2001, Kanaya 2003, McKenzie 2003, Howard 2004, Scott 2004, Kernohan 2007, Andersson 1997, Thunell 2006, Samaras 1999, Friday 2001, Manning 2001, Manwaring 2000, Osmanağaoğlu 2005). 7 cohorts (Ferrara 2001, Ferrara 2003, Newton 2003, Kim 2019, Kane 2008, Di Martino 2004, Codes 2007) 4 case control (Gami 2003, Cushman 2004, Canonico 2006, Vinogradova 2019) 2 cross sectional (Crespo 2002, Sites 2001)
BREAST CANCER	3 trials (Stockholm, HABITS, LIBERATE) 11 cohorts (Marttunen 2001, Vassilopoulou 2002, Decker 2003, Kotsopoulos 2018, Durna 2002, O`Meara 2001, Dew 1998, DiSaia 2000, Beckman 2001, DiSaia 1996, Rebbeck 2005) 2 caso control (Eisen 2008, Kotsopoulos 2016)
OTHER CANCERS	5 trials (Eeles 2015, Li 2012, Guidozzi 1999, Barakat 2006, Ploch 1987) 23 cohorts (Eeles 1991, Mascarenhas 2006, Ursic-Vrscaj 2001, Wen 2013, Power 2016, Zhang 2016, Ayhan 2006, Suriano 2001, Arteaga-Gómez 2011, Creasman 1986, Lee 1990, Chapman 1996, Lim 2018, Cho 2019, Slattery 1999, Mandelson 2003, Chan 2006, Arem 2015, Ji 2018, Ayeni 2009, Huang 2009, Clague 2014, MacKie 2004)

References to the studies assessed

- AGE

Anderson GL, Chlebowski RT, Aragaki AK, Kuller LH, Manson JE, Gass M, Bluhm E, Connelly S, Hubbell FA, Lane D, Martin L, Ockene J, Rohan T, Schenken R, Wactawski-Wende J. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol. 2012 May;13(5):476-86. doi: 10.1016/S1470-2045(12)70075-X.

Chlebowski RT, Anderson GL, Gass M, Lane DS, Aragaki AK, Kuller LH, Manson JE, Stefanick ML, Ockene J, Sarto GE, Johnson KC, Wactawski-Wende J, Ravdin PM, Schenken R, Hendrix SL, Rajkovic A, Rohan TE, Yasmeen S, Prentice RL; WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010 Oct 20;304(15):1684-92. doi: 10.1001/jama.2010.1500.

Kim JE, Chang JH, Jeong MJ, Choi J, Park J, Baek C, Shin A, Park SM, Kang D, Choi JY. A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases. Sci Rep. 2020 Nov 26;10(1):20631. doi: 10.1038/s41598-020-77534-9.

Nudy M, Chinchilli VM, Foy AJ. A systematic review and meta-regression analysis to examine the 'timing hypothesis' of hormone replacement therapy on mortality, coronary heart disease, and stroke. Int J Cardiol Heart Vasc. 2019 Jan 18;22:123-131. doi: 10.1016/j.ijcha.2019.01.001.

Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C,

Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013 Oct 2;310(13):1353-68. doi: 10.1001/jama.2013.278040.

Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Chlebowski RT, Howard BV, Thomson CA, Margolis KL, Lewis CE, Stefanick ML, Jackson RD, Johnson KC, Martin LW, Shumaker SA, Espeland MA, Wactawski-Wende J; WHI Investigators. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA. 2017 Sep 12;318(10):927-938. doi: 10.1001/jama.2017.11217.

Oliver-Williams C, Glisic M, Shahzad S, Brown E, Pellegrino Baena C, Chadni M, Chowdhury R, Franco OH, Muka T. The route of administration, timing, duration and dose of postmenopausal hormone therapy and cardiovascular outcomes in women: a systematic review. Hum Reprod Update. 2019 Mar 1;25(2):257-271. doi: 10.1093/humupd/dmy039

Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ. 2020 Oct 28;371:m3873. doi: 10.1136/bmj.m3873.

Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, Brunner EJ, Kuh D, Hardy R, Avis NE, Gold EB, Derby CA, Matthews KA, Cade JE, Greenwood DC, Demakakos P, Brown DE, Sievert LL, Anderson D, Hayashi K, Lee JS, Mizunuma H, Tillin T, Simonsen MK, Adami HO, Weiderpass E, Mishra GD. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Health. 2019 Nov;4(11):e553-e564. doi: 10.1016/S2468-2667(19)30155-0.

- TEV

Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR; Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. JAMA. 2004 Oct 6;292(13):1573-80. doi: 10.1001/jama.292.13.1573.

Douketis JD, Julian JA, Crowther MA, Kearon C, Bates SM, Barone M, Piovella F, Middeldorp S, Prandoni P, Johnston M, Costantini L, Ginsberg JS. The effect of prothrombotic blood abnormalities on risk of deep vein thrombosis in users of hormone replacement therapy: a prospective case-control study. Clin Appl Thromb Hemost. 2011 Nov-Dec;17(6):E106-13. doi: 10.1177/1076029610387587.

Facchinetti F, Nappi RE, Tirelli A, Polatti F, Nappi G, Sances G. Hormone supplementation differently affects migraine in postmenopausal women. Headache. 2002 Oct;42(9):924-9. doi: 10.1046/j.1526-4610.2002.02215.x. Erratum in: Headache. 2003 Feb;43(2):172. Erratum in: Headache. 2003 Mar;43(3):310.

Herrington DM, Vittinghoff E, Howard TD, Major DA, Owen J, Reboussin DM, Bowden D, Bittner V, Simon JA, Grady D, Hulley SB. Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease. Arterioscler Thromb Vasc Biol. 2002 Jun 1;22(6):1012-7. doi: 10.1161/01.atv.0000018301.91721.94.

Hoibraaten_E, Arnesen_H, Larsen_S, Wickstrom_E, Sandset_PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy: results of the randomized, double blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thrombosis and Haemostasis 2000;84:961-7.

Høibraaten E, Qvigstad E, Andersen TO, Mowinckel MC, Sandset PM. The effects of hormone replacement therapy (HRT) on hemostatic variables in women with previous venous thromboembolism–results from a randomized, double-blind, clinical trial. Thromb Haemost. 2001 May;85(5):775-81. PMID: 11372667.

Lowe G, Woodward M, Vessey M, Rumley A, Gough P, Daly E. Thrombotic variables and risk of idiopathic venous thromboembolism in women aged 45-64 years. Relationships to hormone replacement therapy. Thromb Haemost. 2000 Apr;83(4):530-5. PMID: 10780311.

Li L, Schulz UG, Kuker W, Rothwell PM; Oxford Vascular Study. Age-specific association of migraine with cryptogenic TIA and stroke: Population-based study. Neurology. 2015 Oct 27;85(17):1444-51. doi: 10.1212/WNL.0000000000002059.

Nappi RE, Cagnacci A, Granella F, Piccinini F, Polatti F, Facchinetti F. Course of primary headaches during hormone replacement therapy. Maturitas. 2001 Apr 20;38(2):157-63. doi: 10.1016/s0378-5122(00)00215-2.

Nappi RE, Sances G, Sommacal A, Detaddei S, Facchinetti F, Cristina S, Polatti F, Nappi G. Different effects of tibolone and low-dose EPT in the management of postmenopausal women with primary headaches. Menopause. 2006 Sep-Oct;13(5):818-25. doi: 10.1097/01.gme.0000227399.53192.f5.

Olié V, Plu-Bureau G, Conard J, Horellou MH, Canonico M, Scarabin PY. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause. 2011 May;18(5):488-93.

Rosendaal FR, Vessey M, Rumley A, Daly E, Woodward M, Helmerhorst FM, Lowe GD. Hormonal replacement therapy, prothrombotic mutations and the risk of venous thrombosis. Br J Haematol. 2002 Mar;116(4):851-4. doi: 10.1046/j.0007-1048.2002.03356.x. PMID: 11886391.

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321-33.

Straczek C, Oger E, Yon de Jonage-Canonico MB, Plu-Bureau G, Conard J, Meyer G, Alhenc-Gelas M, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. Circulation. 2005 Nov 29;112(22):3495-500. doi: 10.1161/CIRCULATIONAHA.105.565556.

Excluded studies

did not report disaggregated data for women with previous TEV

Boardman HMP, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, Gabriel Sanchez R, Knight B. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD002229. DOI: 10.1002/14651858.CD002229.pub4.

Did not report data for women with previous TEV

Eischer L, Eichinger S, Kyrle PA. The risk of recurrence in women with venous thromboembolism while using estrogens: a prospective cohort study. J Thromb Haemost. 2014;12(5):635–640.

Kiconco S. Recurrence risk of venous thromboembolism and hormone use in women from England: a cohort study using clinical practice research datalink. Br J Haematol. 2017 Apr;177(1):127-135.

Kyrle PA. The risk of recurrent venous thromboembolism in men and women. N Engl J Med. 2004 Jun 17;350(25):2558-63.

Le Gal G. Risk of recurrent venous thromboembolism after a first oestrogen-associated episode. Data from the REVERSE cohort study. Thromb Haemost. 2010 Sep;104(3):498-503.

Lutsey PL, Virnig BA, Durham SB, Steffen LM, Hirsch AT, Jacobs DR Jr, Folsom AR. Correlates and consequences of venous thromboembolism: The Iowa Women's Health Study. Am J Public Health. 2010 Aug;100(8):1506-13. doi: 10.2105/AJPH.2008.157776.

- TOBACCO

Malek AM, Vladutiu CJ, Meyer ML, Cushman M, Newman R, Lisabeth LD, Kleindorfer D, Lakkur S, Howard VJ. The association of age at menopause and all-cause and cause-specific mortality by race, postmenopausal hormone use, and smoking status. Prev Med Rep. 2019;15:100955. doi: 10.1016/j.pmedr.2019.100955.

Mann RD, Lis Y, Chukwujindu J, Chanter DO. A study of the association between hormone replacement therapy, smoking and the occurrence of myocardial infarction in women. J Clin Epidemiol. 1994;47(3):307-12. doi: 10.1016/0895-4356(94)90014-0

Wilson PW, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study. N Engl J Med. 1985;313(17):1038-43. doi: 10.1056/NEJM198510243131702.

Excluded studies

Reviews

Mueck AO, Seeger H. Smoking, estradiol metabolism and hormone replacement therapy. Curr Med Chem Cardiovasc Hematol Agents. 2005 Jan;3(1):45-54. doi: 10.2174/1568016052773270.

Ruan X, Mueck AO. Impact of smoking on estrogenic efficacy. Climacteric. 2015 Feb;18(1):38-46. doi: 10.3109/13697137.2014.929106.

Did not report data on the impact of treatment for smokers and no smokers

Li S, Rosenberg L, Wise LA, Boggs DA, LaValley M, Palmer JR. Age at natural menopause in relation to all-cause and cause-specific mortality in a follow-up study of US black women. Maturitas. 2013;75(3):246-52. doi: 10.1016/j.maturitas.2013.04.003.

Assessed surrogate outcomes (lipids, oestrogen metabolism, haemodynamic variables)

Beljic T, Babic DT, Babi D, Knezevic N, Drezgic M. Effect of hormone replacement therapy on lipids and left ventricular function in postmenopausal smokers. Climacteric. 2004 Dec;7(4):366-74. doi: 10.1080/13697130400001778.

Cassidenti DL, Vijod AG, Vijod MA, Stanczyk FZ, Lobo RA. Short-term effects of smoking on the pharmacokinetic profiles of micronized estradiol in postmenopausal women. Am J Obstet Gynecol. 1990;163(6 Pt 1):1953-60. doi: 10.1016/0002-9378(90)90780-b.

Driul L, Stella A, Marchesoni D. Twenty-four hour ambulatory blood pressure in postmenopausal smokers and non-smokers on hormone therapy. Int J Gynaecol Obstet. 2005 Jul;90(1):82-3. doi: 10.1016/j.ijgo.2005.02.023

Geisler J, Omsjø IH, Helle SI, Ekse D, Silsand T, Lønning PE. Plasma oestrogen fractions in postmenopausal women receiving hormone replacement therapy: influence of route of administration and cigarette smoking. J Endocrinol. 1999;162(2):265-70. doi: 10.1677/joe.0.1620265.

Girdler SS, Hinderliter AL, West SG, Grewen K, Steege J, Light KC. Postmenopausal smokers show reduced hemodynamic benefit from oral hormone replacement. Am J Cardiol. 2000;86(5):590-2, A10. doi: 10.1016/s0002-9149(00)01027-4.

Girdler SS, Hinderliter AL, Wells EC, Sherwood A, Grewen KM, Light KC. Transdermal versus oral estrogen therapy in postmenopausal smokers: hemodynamic and endothelial effects. Obstet Gynecol. 2004 Jan;103(1):169-80. doi: 10.1097/01.AOG.0000103998.48122.0b.

Jensen J, Christiansen C, Rødbro P. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. N Engl J Med. 1985;313(16):973-5. doi: 10.1056/NEJM198510173131602.

Jensen J, Christiansen C. Effects of smoking on serum lipoproteins and bone mineral content during postmenopausal hormone replacement therapy. Am J Obstet Gynecol. 1988;159(4):820-5. doi: 10.1016/s0002-9378(88)80144-3.

Mancini F, Persico N, Genazzani AD, Volpe A, Battaglia C, De Aloysio D. Effects of hormone replacement therapy on plasma viscosity and Doppler variations in postmenopausal non-smokers and heavy smokers. Gynecol Endocrinol. 2005 Apr;20(4):221-6. doi: 10.1080/09513590400027281.

Sriprasert I, Kono N, Karim R, Hodis HN, Stanczyk FZ, Shoupe D, Mack WJ. Factors Associated With Serum Estradiol Levels Among Postmenopausal Women Using Hormone Therapy. Obstet Gynecol. 2020;136(4):675-684. doi: 10.1097/AOG.0000000000004006.

- CV DISEASE

Alexander KP, Newby LK, Hellkamp AS, Harrington RA, Peterson ED, Kopecky S, Langer A, O'Gara P, O'Connor CM, Daly RN, Califf RM, Khan S, Fuster V. Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up. J Am Coll Cardiol. 2001 Jul;38(1):1-7. doi: 10.1016/s0735-1097(01)01329-8

Angeja BG, Shlipak MG, Go AS, Johnston SC, Frederick PD, Canto JG, Barron HV, Grady D; National Registry of Myocardial Infarction 3 Investigators. Hormone therapy and the risk of stroke after acute myocardial infarction in postmenopausal women. J Am Coll Cardiol. 2001 Nov 1;38(5):1297-301. doi: 10.1016/s0735-1097(01)01551-0.

Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Hormone replacement therapy and adverse outcomes in women with atrial fibrillation: an analysis from the atrial fibrillation follow-up investigation of rhythm management trial. Stroke. 2014 Oct;45(10):3076-9.

Bretler DM, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C, Jensen TB, Raunsø J, Torp-Pedersen C, Gislason GH. Hormone replacement therapy and risk of new-onset atrial fibrillation after myocardial infarction–a nationwide cohort study. PLoS One. 2012;7(12):e51580. doi: 10.1371/journal.pone.0051580.

Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofiel PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. BJOG. 2002 Sep;109(9):1056-62. doi: 10.1111/j.1471-0528.2002.01544.x

Collins P, Flather M, Lees B, Mister R, Proudler A, Stevenson JC, WHISP (Women's Hormone Intervention Secondary Prevention Study) Pilot Study Investigators. Randomized trial of effects of continuous combined HRT on markers of lipids and coagulation in women with acute coronary syndromes: WHISP Pilot Study. European Heart Journal 2006;27(17):2046-53.

ESPRIT Team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. Lancet 2002;360:2001-8.

Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley S, et al. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and

baseline characteristics. Controlled Clinical Trials 1998;19(4):314-35.

Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the nurses' health study. a prospective, observational study. Ann Intern Med. 2001; 135:1–8.

Herrington DM, Reboussin DM, Bridget Brosnihan K, Sharp PC, Shumaker SA, Snyder TE, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. New England Journal of Medicine 2000;343(8):522-9.

Hodis HN, Mack WJ, Azen SP, Lobo RA, Shoupe D, Mahrer PR, et al. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. New England Journal of Medicine 2003;349(6):535-45.

Khan MA, Liu MW, Singh D, Pal A, Chio FL, Lawson D, Dean LS. Long-term (three years) effect of estrogen replacement therapy on major adverse cardiac events in postmenopausal women after intracoronary stenting. Am J Cardiol. 2000 Aug 1;86(3):330-3. doi: 10.1016/s0002-9149(00)00926-7.

Lindenfeld J, Ghali JK, Krause-Steinrauf HJ, Khan S, Adams K, Goldman S, Peberdy MA, Yancy C, Thaneemit-Chen S, Larsen RL, Young J, Lowes B, Rosenberg YD; BEST Investigators. Hormone replacement therapy is associated with improved survival in women with advanced heart failure. J Am Coll Cardiol. 2003 Oct 1;42(7):1238-45.

Nussmeier NA, Marino MR, Vaughn WK. Hormone replacement therapy is associated with improved survival in women undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2002 Dec;124(6):1225-9.Ouyang P, Tardif J, Herrington D, Stewart K, Thompson P, Walsh M, et al. Randomized trial of hormone therapy in women after coronary bypass surgery: Evidence of differential effect of hormone therapy on angiographic progression of disease in saphenous vein grafts and native coronary arteries. Atherosclerosis 2006;189(2):375-86.

Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. New England Journal of Medicine 2001;345(17):1243-9.

Waters D, Alderman E, Hsia J, Howard B, Cobb F, Rogers W, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women. JAMA 2001;288(19):2432-40.

Excluded studies

Reviews

Boardman HMP, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, Gabriel Sanchez R, Knight B. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD002229. DOI: 10.1002/14651858.CD002229.pub4.

- METABOLIC SYNDROME

Andersson B, Mattsson LA, Hahn L, Mårin P, Lapidus L, Holm G, Bengtsson BA, Björntorp P. Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1997 Feb;82(2):638-43.

Brussaard HE, Gevers Leuven JA, Frölich M, Kluft C, Krans HM. Short-term oestrogen replacement therapy improves insulin resistance, lipids and fibrinolysis in postmenopausal women with NIDDM. Diabetologia 1997;40(7):843-9. doi:10.1007/s001250050758.

Canonico M, Oger E, Conard J, Meyer G, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY; EStrogen and THromboEmbolism Risk (ESTHER) Study Group. Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. J Thromb Haemost. 2006 Jun;4(6):1259-65. doi: 10.1111/j.1538-7836.2006.01933.x.

Cornu C, Mercier C, Ffrench P, et al. Postmenopause hormone treatment in women with NIDDM or impaired glucose tolerance: the MEDIA randomized clinical trial. Maturitas. 2000;37(2):95-104. doi:10.1016/s0378-5122(00)00164-x.

Crespo CJ, Smit E, Snelling A, Sempos CT, Andersen RE; NHANES III. Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care. 2002 Oct;25(10):1675-80. doi: 10.2337/diacare.25.10.1675.

Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR; Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. JAMA. 2004 Oct 6;292(13):1573-80. doi: 10.1001/jama.292.13.1573. PMID: 15467059

Ferrara A. Current use of unopposed estrogen and estrogen plus progestin and the risk of acute myocardial infarction among women with diabetes: the Northern California Kaiser Permanent Diabetes Registry, 1995-8. Circulation. 2003 Jan 7;107(1):43-8.

Friday KE, Dong C, Fontenot RU. Conjugated equine estrogen improves glycemic control and blood lipoproteins in postmenopausal women with type 2 diabetes. J Clin Endocrinol Metab. 2001;86(1):48-52. doi:10.1210/jcem.86.1.7094

Gami AS, Wright RS, Ballman KV, Kopecky SL, Hayes SN. Hormone replacement therapy and risk of acute myocardial infarction in postmenopausal women with diabetes mellitus. *Am J Cardiol.* 2003;91(10):1275-7. doi:10.1016/s0002-9149(03)00284-4.

Howard BV. Postmenopausal hormone therapy is associated with atherosclerosis progression in women with abnormal glucose tolerance. Circulation. 2004 Jul 13;110(2):201-6.Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2003;138:1e9.

Kernohan AF, Sattar N, Hilditch T, Cleland SJ, Small M, Lumsden MA, et al. Effects of low-dose continuous combined hormone replacement therapy on glucose homeostasis and markers of cardiovascular risk in women with type 2 diabetes. Clin Endocrinol (Oxf) 2007;66:27e34.

Kim JE, Choi J, Park J, Lee JK, Shin A, Park SM, Kang D, Choi JY. Associations of postmenopausal hormone therapy with metabolic syndrome among diabetic and non-diabetic women. Maturitas. 2019 Mar;121:76-82. doi: 10.1016/j.maturitas.2018.12.012. Epub 2018 Dec 20. PMID: 30704569.

Manning PJ, Allum A, Jones S, Sutherland WH, Williams SM. The effect of hormone replacement therapy on cardiovascular risk factors in type 2 diabetes: a randomized controlled trial. Arch Intern Med 2001;161(14):1772-6. doi:10.1001/archinte.161.14.1772.

Manwaring P, Morfis L, Diamond T, Howes LG. The effects of hormone replacement therapy on plasma lipids in type II diabetes. Maturitas. 2000 Mar 31;34(3):239-47. doi: 10.1016/s0378-5122(99)00112-7.

McKenzie J, Jaap AJ, Gallacher S, Kelly A, Crawford L, Greer IA, et al. Metabolic, inflammatory and haemostatic effects of a low-dose continuous combined HRT in women with type 2 diabetes: potentially safer with respect to vascular risk? Clin Endocrinol (Oxf) 2003;59:682e9.

Mosnier-Pudar H, Faguer B, Guyenne TT, Tchobroutsky G. Effets de la substitution par 17 beta estradiol percutané et progestérone orale sur la pression artérielle et les paramètres métaboliques chez des patientes ménopausées diabétiques non insulinodépendantes [Effects of deprivation and

replacement by percutaneous 17 beta estradiol and oral progesterone on blood pressure and metabolic parameters in menopause patients with non-insulin-dependent diabetes]. Arch Mal Coeur Vaiss. 1991;84(8):1111-5.

Newton KM, LaCroix AZ, Heckbert SR, Abraham L, McCulloch D, Barlow W. Estrogen therapy and risk of cardiovascular events among women with type 2 diabetes. *Diabetes Care*. 2003;26(10):2810-6. doi:10.2337/diacare.26.10.2810.

Osmanağaoğlu MA, Osmanağaoğlu S, Osmanağaoğlu T, Okumuş B, Bozkaya H. Effect of different preparations of hormone therapy on lipid and glucose metabolism, coagulation factors, and bone mineral density in overweight and obese postmenopausal women. Fertil Steril. 2005;84(2):384–93.

Scott AR, Dhindsa P, Forsyth J, Mansell P. Effect of hormone replacement therapy on cardiovascular risk factors in postmenopausal women with diabetes. Diabetes, Obesity and Metabolism 2004;6:16-22.

Sites CK, Brochu M, Tchernof A, Poehlman ET. Relationship between hormone replacement therapy use with body fat distribution and insulin sensitivity in obese postmenopausal women. Metabolism. 2001;50(7):835–40.

Sutherland WH, Manning PJ, de Jong SA, Allum AR, Jones SD, Williams SM. Hormone-replacement therapy increases sèrum paraoxonase arylesterase activity in diabetic postmenopausal women. Metabolism 2001;50:319e24.

Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019 Jan 9;364:k4810. doi: 10.1136/bmj.k4810. Erratum in: BMJ. 2019 Jan 15;364:l162.

Excluded studies

Reviews

Mackay L, Kilbride L, Adamson KA, Chisholm J. Hormone replacement therapy for women with type 1 diabetes mellitus. Cochrane Database Syst Rev. 2013;(6):CD008613. Published 2013 Jun 6. doi:10.1002/14651858.CD008613.pub2.

Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab. 2006;8(5):538-54. doi:10.1111/j.1463-1326.2005.00545.x.

Xu Y, Lin J, Wang S, Xiong J, Zhu Q. Combined estrogen replacement therapy on metabolic control in postmenopausal women with diabetes mellitus. Kaohsiung J Med Sci. 2014;30(7):350-61. doi:10.1016/j.kjms.2014.03.002.

Did not include an inactive control group

Araújo DA, Farias ML, Andrade AT. Effects of transdermal and oral estrogen replacement on lipids and glucose metabolism in postmenopausal women with type 2 diabetes mellitus. Climacteric. 2002;5(3):286–92.

Xue W, Deng Y, Wang YF, Sun AJ. Effect of Half-dose and Standard-dose Conjugated Equine Estrogens Combined with Natural Progesterone or Dydrogesterone on Components of Metabolic Syndrome in Healthy Postmenopausal Women: A Randomized Controlled Trial. Chin Med J (Engl). 2016 Dec 5;129(23):2773-2779. doi: 10.4103/0366-6999.194646.

Non-eligible design

Sumino H. Hormone replacement therapy decreases insulin resistance and lipid metabolism in Japanese postmenopausal women with impaired and normal glucose tolerance. Horm Res. 2003;60(3):134-42.

Non-eligible outcomes

Darko DA, Dornhorst A, Kennedy G, Mandeno RC, Seed M. Glycaemic control and plasma lipoproteins in menopausal women with Type 2 diabetes treated with oral and transdermal combined hormone replacement therapy. Diabetes Res Clin Pract 2000, 54 (3), 157-64. Xllth International Symposium on Atherosclerosis, Stockholm, Sweden, June 25-29, 2000. doi:https://doi.org/10.1016/S0168-8227(01)00297-2.

Lamon-Fava S, Herrington DM, Horvath KV, Schaefer EJ, Asztalos BF. Effect of hormone replacement therapy on plasma lipoprotein levels and coronary atherosclerosis progression in postmenopausal women according to type 2 diabetes mellitus status. Metabolism 2010;59:1794e800.

Perera M, Sattar N, Petrie JR, et al. The effects of transdermal estradiol in combination with oral norethisterone on lipoproteins, coagulation, and endothelial markers in postmenopausal women with type 2 diabetes: a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2001;86 (3):1140–3. doi:10.1210/jcem.86.3.7297.

Sánchez-Rodríguez MA, Zacarías-Flores M, Castrejón-Delgado L, Ruiz-Rodríguez AK, Mendoza-Núñez VM. Effects of Hormone Therapy on Oxidative Stress in Postmenopausal Women with Metabolic Syndrome. Int J Mol Sci. 2016 Aug 24;17(9):1388. doi: 10.3390/ijms17091388.

- DIGESTIVE DISEASES

Codes L, Asselah T, Cazals-Hatem D, Tubach F, Vidaud D, Paraná R, Bedossa P, Valla D, Marcellin P. Liver fibrosis in women with chronic hepatitis C: evidence for the negative role of the menopause and steatosis and the potential benefit of hormone replacement therapy. Gut. 2007 Mar;56(3):390-5. doi: 10.1136/gut.2006.101931.

Di Martino V. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology. 2004 Dec;40 (6):1426-33.

Kane SV. Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease. Am J Gastroenterol. 2008 May;103(5):1193-6.

Excluded studies

Non-eligible population

Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, Larson JC. Effect of estrogen therapy on gallbladder disease. JAMA. 2005 Jan 19;293(3):330-9. doi: 10.1001/jama.293.3.330. PMID: 15657326.

Khalili H, Higuchi LM, Ananthakrishnan AN, Manson JE, Feskanich D, Richter JM, Fuchs CS, Chan AT. Hormone therapy increases risk of ulcerative colitis but not Crohn's disease. Gastroenterology. 2012 Nov;143(5):1199-1206. doi: 10.1053/j.gastro.2012.07.096

Simon JA, Hunninghake DB, Agarwal SK, Lin F, Cauley JA, Ireland CC, Pickar JH. Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med. 2001 Oct 2;135(7):493-501. doi: 10.7326/0003-4819-135-7-200110020-00008.

Schwarz S, Völzke H, Baumeister SE, Hampe J, Dören M. Menopausal hormone therapy and gallbladder disease: the Study of Health in Pomerania (SHIP). Clin Endocrinol (Oxf). 2007 Jul;67(1):51-9. doi: 10.1111/j.1365-2265.2007.02834.x.

Non-eligible outcolist mes

Rinaldi M, Cagnacci A, Pansini FE, de Aloysio D, Sgarabotto MP, Bacchi-Modena A. Neutral effect of prolonged transdermal hormone therapy on liver function of postmenopausal women with chronic active hepatitis. Menopause. 2005 Sep-Oct;12(5):619-22.

Clements D, Compston JE, Evans WD, Rhodes J. Hormone replacement therapy prevents bone loss in patients with inflammatory bowel disease. Gut. 1993 Nov;34(11):1543-6. doi: 10.1136/gut.34.11.1543. PMID: 8244141

- BREAST CANCER

Beckmann MW, Jap D, Djahansouzi S, Nestle-Krämling C, Kuschel B, Dall P, Brumm C, Bender HG. Hormone replacement therapy after treatment of breast cancer: effects on postmenopausal symptoms, bone mineral density and recurrence rates. Oncology. 2001;60(3):199-206.

Decker DA, Pettinga JE, VanderVelde N, Huang RR, Kestin L, Burdakin JH. Estrogen replacement therapy in breast cancer survivors: a matched-controlled series. Menopause. 2003 Jul-Aug;10(4):277-85.

Dew J, Eden J, Beller E, Magarey C, Schwartz P, Crea P, Wren B. A cohort study of hormone replacement therapy given to women previously treated for breast cancer. Climacteric. 1998 Jun;1(2):137-42.

DiSaia PJ, Grosen EA, Kurosaki T, Gildea M, Cowan B, Anton-Culver H. Hormone replacement therapy in breast cancer survivors: a cohort study. Am J Obstet Gynecol. 1996 May;174(5):1494-8.

DiSaia PJ, Brewster WR, Ziogas A, Anton-Culver H. Breast cancer survival and hormone replacement therapy: a cohort analysis. Am J Clin Oncol. 2000 Dec;23(6):541-5.

Durna EM, Wren BG, Heller GZ, Leader LR, Sjoblom P, Eden JA. Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. Med J Aust. 2002 Oct 7;177(7):347-51.

Eisen A, Lubinski J, Gronwald J, Moller P, Lynch HT, Klijn J, Kim-Sing C, Neuhausen SL, Gilbert L, Ghadirian P, Manoukian S, Rennert G, Friedman E, Isaacs C, Rosen E, Rosen B, Daly M, Sun P, Narod SA; Hereditary Breast Cancer Clinical Study Group. Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers. J Natl Cancer Inst. 2008 Oct 1;100(19):1361-7. doi: 10.1093/jnci/djn313.

Holmberg L, Anderson H; HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer–is it safe?), a randomised comparison: trial stopped. Lancet. 2004 Feb 7;363(9407):453-5.

Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Sellin R, Yip CH, Egberts J, Mol-Arts M, Mulder R, van Os S, Beckmann MW; LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol. 2009 Feb;10(2):135-46. doi: 10.1016/S1470-2045(08)70341-3.

Kotsopoulos J, Huzarski T, Gronwald J, Moller P, Lynch HT, Neuhausen SL, Senter L, Demsky R, Foulkes WD, Eng C, Karlan B, Tung N, Singer CF, Sun P, Lubinski J, Narod SA. Hormone replacement therapy after menopause and risk of breast cancer in BRCA1 mutation carriers: a case-control study. Breast Cancer Res Treat. 2016 Jan;155(2):365-73. doi: 10.1007/s10549-016-3685-3.

Kotsopoulos J, Gronwald J, Karlan BY, Huzarski T, Tung N, Moller P, Armel S, Lynch HT, Senter L, Eisen A, Singer CF, Foulkes WD, Jacobson MR, Sun P, Lubinski J, Narod SA; Hereditary Breast Cancer Clinical Study Group. Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers. JAMA Oncol. 2018 Aug 1;4(8):1059-1065. doi: 10.1001/jamaoncol.2018.0211.

Marttunen MB, Hietanen P, Pyrhönen S, Tiitinen A, Ylikorkala O. A prospective study on women with a history of breast cancer and with or without estrogen replacement therapy. Maturitas. 2001 Sep 28;39(3):217-25.

O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. J Natl Cancer Inst. 2001 May 16;93(10):754-62.

Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, van 't Veer L, Eeles R, Evans DG, Tomlinson G, Matloff E, Narod SA, Eisen A, Domchek S, Armstrong K, Weber BL; PROSE Study Group. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2005 Nov 1;23(31):7804-10. doi: 10.1200/JCO.2004.00.8151. Epub 2005 Oct 11. PMID: 16219936.

Vassilopoulou-Sellin R, Cohen DS, Hortobagyi GN, Klein MJ, McNeese M, Singletary SE, Smith TL, Theriault RL. Estrogen replacement therapy for menopausal women with a history of breast carcinoma: results of a 5-year, prospective study. Cancer. 2002 Nov 1;95(9):1817-26.

von Schoultz E, Rutqvist LE; Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. J Natl Cancer Inst. 2005 Apr 6;97(7):533-5.

Excluded studies

Reviews

Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. Breast Cancer Res. 2005;7(4):R535-40.

Mudhune GH, Armour M, McBride KA. Safety of menopausal hormone therapy in breast cancer survivors older than fifty at diagnosis: A systematic review and meta-analysis. Breast. 2019 Oct;47:43-55. doi: 10.1016/j.breast.2019.06.002.

Wang Y, Lewin N, Qaoud Y, Rajaee AN, Scheer AS. The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: A systematic review. Breast. 2018 Aug;40:123-130. doi: 10.1016/j.breast.2018.05.002.

Yu X, Zhou S, Wang J, Zhang Q, Hou J, Zhu L, He Y, Zhao J, Zhong S. Hormone replacement therapy and breast cancer survival: a systematic review and meta-analysis of observational studies. Breast Cancer. 2017 Sep;24(5):643-657. doi: 10.1007/s12282-017-0789-5.

Non-eligible designs

Kroiss R, Fentiman IS, Helmond FA, Rymer J, Foidart JM, Bundred N, Mol-Arts M, Kubista E. The effect of tibolone in postmenopausal women receiving tamoxifen after surgery for breast cancer: a randomised, double-blind, placebo-controlled trial. BJOG. 2005 Feb;112(2):228-33. doi: 10.1111/j.1471-0528.2004.00309.x.

Ursic-Vrscaj M, Bebar S. A case-control study of hormone replacement therapy after primary surgical breast cancer treatment. Eur J Surg Oncol. 1999 Apr;25(2):146-51.

Non-eligible treatments

Le Ray I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S. Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. Breast Cancer Res Treat. 2012 Sep;135(2):603-9. doi: 10.1007/s10549-012-2198-y.

Natrajan PK, Soumakis K, Gambrell RD Jr. Estrogen replacement therapy in women with previous breast cancer. Am J Obstet Gynecol. 1999

Aug;181(2):288-95.

Reeves GK, Patterson J, Vessey MP, Yeates D, Jones L. Hormonal and other factors in relation to survival among breast cancer patients. Int J Cancer. 2000 May 20;89(3):293-9.

Non-evaluable data

Marsden J, Whitehead M, A'Hern R, Baum M, Sacks N. Are randomized trials of hormone replacement therapy in symptomatic women with breast cancer feasible? Fertil Steril. 2000 Feb;73(2):292-9.

- OTHER CANCERS

Arem H, Park Y, Felix AS, Zervoudakis A, Brinton LA, Matthews CE, Gunter MJ. Reproductive and hormonal factors and mortality among women with colorectal cancer in the NIH-AARP Diet and Health Study. Br J Cancer. 2015 Jul 28;113(3):562-8. doi: 10.1038/bjc.2015.224.

Arteaga-Gómez AC, Castellanos-Barroso G, Colin-Valenzuela A, García-Vargas J, Márquez-Acosta G, Reyes-Muñoz E. [Hormone therapy effect in postmenopausal women with history of endometrial cancer]. Ginecol Obstet Mex. 2011 Jan;79(1):11-7.

Ayeni O, Robinson A. Hormone replacement therapy and outcomes for women with non-small-cell lung cancer: can an association be confirmed? Curr Oncol. 2009 May;16(3):21-5.

Ayhan A, Taskiran C, Simsek S, Sever A. Does immediate hormone replacement therapy affect the oncologic outcome in endometrial cancer survivors? Int J Gynecol Cancer 2006;16:805–8.

Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS, Gynecologic Oncology Group Study. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. Journal of Clinical Oncology 2006;24(4):587-92.

Clague J, Reynolds P, Henderson KD, Sullivan-Halley J, Ma H, Lacey JV Jr, Chang S, Delclos GL, Du XL, Forman MR, Bernstein L. Menopausal hormone therapy and lung cancer-specific mortality following diagnosis: the California Teachers Study. PLoS One. 2014 Jul 31;9(7):e103735. doi: 10.1371/journal.pone.0103735.

Creasman WT, Henderson D, Hinshaw W, Clarke-Pearson DL. Estrogen replacement therapy in the patient treated for endometrial cancer. Obstet Gynecol 1986;67:326–30.

Chan JA, Meyerhardt JA, Chan AT, Giovannucci EL, Colditz GA, Fuchs CS. Hormone replacement therapy and survival after colorectal cancer diagnosis. J Clin Oncol. 2006 Dec 20;24(36):5680-6.

Chapman JA, DiSaia PJ, Osann K, Roth PD, Gillotte DL, Berman ML. Estrogen replacement in surgical stage I and II endometrial cancer survivors. Am J Obstet Gynecol 1996;175:1195–200.

Cho HW, Ouh YT, Lee JK, Hong JH. Effects of hormone therapy on recurrence in endometrial cancer survivors: a nationwide study using the Korean Health Insurance Review and Assessment Service database. J Gynecol Oncol. 2019 Jul;30(4):e51. doi: 10.3802/jgo.2019.30.e51.

Eeles RA, Tan S, Wiltshaw E, et al. Hormone replacement therapy and survival after surgery for ovarian cancer. BMJ 1991;302:259-262.

Eeles RA, Morden JP, Gore M, Mansi J, Glees J, Wenxzl M, et al. Adjuvant hormone therapy may improve survival in epithelial ovarian cancer: results of the AHT Randomized Trial. Journal of Clinical Oncology 2015;33(35):4138-44. [DOI: 10.1200/JCO.2015.60.9719]

Guidozzi F, Daponte A. Estrogen replacement therapy for ovarian carcinoma survivors: a randomized controlled trial. Cancer 1999;86(6):1013-8.

Huang B, Carloss H, Wyatt SW, Riley E. Hormone replacement therapy and survival in lung cancer in postmenopausal women in a rural population. Cancer. 2009 Sep 15;115(18):4167-75. doi: 10.1002/cncr.24475.

Ji J, Sundquist J, Sundquist K. Use of hormone replacement therapy improves the prognosis in patients with colorectal cancer: A population-based study in Sweden. Int J Cancer. 2018 May 15;142(10):2003-2010. doi: 10.1002/ijc.31228.

Lee RB, Burke TW, Park RC. Estrogen replacement therapy following treatment for stage I endometrial carcinoma. Gynecol Oncol 1990;36:189–91.

Li L, Pan Z, Gao K, Zhang W, Luo Y, Yao Z, et al. Impact of postoperative hormone replacement therapy on life quality and prognosis in patients with ovarian malignancy. Oncology Letters 2012;3(1):244-9.

Lim S, Kim YH, Lee KB, Lee JM. The influence of hormone therapy with drospirenone-estradiol on endometrioid type endometrial cancer patients. J Gynecol Oncol. 2018 Sep;29(5):e72. doi: 10.3802/jgo.2018.29.e72.

Mandelson MT, Miglioretti D, Newcomb PA, Harrison R, Potter JD. Hormone replacement therapy in relation to survival in women diagnosed with colon cancer. Cancer Causes Control. 2003 Dec;14(10):979-84.

Mascarenhas C, Lambe M, Bellocco R, et al. Use of hormone replacement therapy before and after ovarian cancer diagnosis and ovarian cancer survival. Int J Cancer 2006;119:2907-2915.

MacKie RM, Bray CA. Hormone replacement therapy after surgery for stage 1 or 2 cutaneous melanoma. Br J Cancer 2004;90(4):770–2.

Ploch E. Hormone replacement therapy in patients after cervical cancer treatment. Gynecol. Oncol 1987;26:169–77.

Power L, Lefas G, Lambert P, Kim D, Evaniuk D, Lotocki R, Dean E, Nachtigal MW, Altman AD. Hormone Use After Nonserous Epithelial Ovarian Cancer: Overall and Disease-Free Survival. Obstet Gynecol. 2016 May;127(5):837-47.

Slattery ML, Anderson K, Samowitz W, Edwards SL, Curtin K, Caan B, Potter JD. Hormone replacement therapy and improved survival among postmenopausal women diagnosed with colon cancer (USA). Cancer Causes Control. 1999 Oct;10(5):467-73.

Suriano KA, McHale M, McLaren CE, Li KT, Re A, DiSaia PJ. Estrogen replacement therapy in endometrial cancer patients: a matched control study. Obstet Gynecol 2001;97:555–60.

Ursic-Vrscaj M, Bebar S, Zakelj MP. Hormone replacement therapy after invasive ovarian serous cystadenocarcinoma treatment: the effect on survival. Menopause 2001;8:70-75.

Wen Y, Huang H, Huang H, Wu M, Shen K, Pan L. The safety of postoperative hormone replacement therapy in epithelial ovarian cancer patients in China. Climacteric 2013;16:673-681.

Zhang YL, Chen JH, Lu W, Li BL, Zhu QY, Wan XP. Efficacy of Postoperative Hormone Replacement Therapy on Prognosis of Patients with Serous Ovarian Carcinoma. Chin Med J (Engl). 2016 Jun 5;129(11):1316-21.

Excluded studies

Reviews

Angioli R, Luvero D, Armento G, Capriglione S, Plotti F, Scaletta G, Lopez S, Montera R, Gatti A, Serra GB, Benedetti Panici P, Terranova C. Hormone replacement therapy in cancer survivors: Utopia? Crit Rev Oncol Hematol. 2018 Apr;124:51-60.

Deli T, Orosz M, Jakab A. Hormone Replacement Therapy in Cancer Survivors - Review of the Literature. Pathol Oncol Res. 2019 Jan 8. pii:

10.1007/s12253-018-00569-x.

Edey KA, Rundle S, Hickey M. Hormone replacement therapy for women previously treated for endometrial cancer. Cochrane Database Syst Rev. 2018 May 15;5:CD008830.

Jang YC, Huang HL, Leung CY. Association of hormone replacement therapy with mortality in colorectal cancer survivor: a systematic review and meta-analysis. BMC Cancer. 2019 Dec 9;19(1):1199. doi: 10.1186/s12885-019-6428-0.

Li D, Ding CY, Qiu LH. Postoperative hormone replacement therapy for epithelial ovarian cancer patients: a systematic review and meta-analysis. Gynecol Oncol. 2015 Nov;139(2):355-62.

O'Donnell RL, Clement KM, Edmondson RJ. Hormone replacement therapy after treatment for a gynaecological malignancy. Curr Opin Obstet Gynecol. 2016 Feb;28(1):32-41. doi: 10.1097/GCO.0000000000000238.

Pergialiotis V, Pitsouni E, Prodromidou A, Frountzas M, Perrea DN, Vlachos GD. Hormone therapy for ovarian cancer survivors: systematic review and meta-analysis. Menopause. 2016 Mar;23(3):335-42.

Saeaib_N, Peeyananjarassri_K, Liabsuetrakul_T, Buhachat_R, Myriokefalitaki_E. Hormone replacement therapy after surgery for epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD012559. DOI: 10.1002/14651858.CD012559.pub2.

Shim SH, Lee SJ, Kim SN. Effects of hormone replacement therapy on the rate of recurrence in endometrial cancer survivors: a meta-analysis. Eur J Cancer. 2014 Jun;50(9):1628-37.

References

[1] T.J. de Villiers, J.E. Hall, J.V. Pinkerton, S.C. Pérez, M. Rees, C. Yang, D. D. Pierroz, Revised global consensus statement on menopausal hormone therapy, Maturitas 91 (2016) 153–155.

[2] I. Lambrinoudaki, E. Armeni, D. Goulis, S. Bretz, I. Ceausu, F. Durmusoglu, R. Erkkola, I. Fistonic, M. Gambacciani, M. Geukes, H. Hamoda, C. Hartley, A. L. Hirschberg, B. Meczekalski, N. Mendoza, A. Mueck, A. Smetnik, P. Stute, M. van Trotsenburg, M. Rees, Menopause, wellbeing and health: a care pathway from the European Menopause and Andropause Society, Maturitas 163 (2022) 1–14.

[3] R.J. Baber, N. Panay, A. Fenton, IMS Writing Group, IMS Recommendations on women's midlife health and menopause hormone therapy, Climacteric 2016 19 (2) (2016) 109–150.

[4] The, hormone therapy position statement of The North American Menopause Society, Menopause 2018 25 (11) (2017) 1362–1387.

[5] 4th ed (Ed.), Medical Eligibility Criteria for Contraceptive Use: A WHO Family Planning Cornerstone, World Health Organization, Geneva, 2010. PMID: 23741782.

[6] N. Mendoza, I. Ramírez, E. De la Viuda, J.C. Vázquez, I. Solà, Cano A on belhaf of the "HMT Elegibility Criteria Group", Eligibility criteria for Menopausal Hormone Therapy (MHT): a consortium of scientific societies for the use of MHT in women with medical conditions. Research protocol, Maturitas 148 (2021 Jun) 14–17.

[7] J.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page, V.A. Welch (Eds.), Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition, John Wiley & Sons, Chichester (UK), 2019.

[8] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009), e1000097, https://doi.org/10.1371/journal.pmed.1000097. PMID: 19621072.

[9] J.A. Sterne, M.A. Hernán, B.C. Reeves, J. Savović, N.D. Berkman, M. Viswanathan, D. Henry, D.G. Altman, M.T. Ansari, I. Boutron, J.R. Carpenter, A.W. Chan, R. Churchill, J.J. Deeks, A. Hróbjartsson, J. Kirkham, P. Jüni, Y. K. Loke, T.D. Pigott, C.R. Ramsay, D. Regidor, H.R. Rothstein, L. Sandhu, P. L. Santaguida, H.J. Schünemann, B. Shea, I. Shrier, P. Tugwell, L. Turner, J. C. Valentine, H. Waddington, E. Waters, G.A. Wells, P.F. Whiting, J.P. Higgins, ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions, BMJ 355 (2016), i4919.

[10] G.H. Guyatt, A.D. Oxman, N. Santesso, M. Helfand, G. Vist, R. Kunz, J. Brozek, S. Norris, J. Meerpohl, B. Djulbegovic, P. Alonso-Coello, P.N. Post, J.W. Busse, P. Glasziou, R. Christensen, H.J. Schünemann, GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes, J. Clin. Epidemiol. 66 (2) (2013) 158–172.

[11] Manager (RevMan) [Computer program], Version 5.4, The Cochrane Collaboration, 2020.

[12] H. Schünemann, J. Brożek, G. Guyyat, A. Oxman, Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach, Updated October 2013. Available from, https://gdt.gradepro.org/app/handbook/handbook.html.

[13] P. Alonso-Coello, H.J. Schünemann, J. Moberg, R. Brignardello-Petersen, E. A. Akl, M. Davoli, et al., GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to 12 www.eurosurveillance.org making well informed healthcare choices. 1: Introduction, BMJ 353 (2016), i2016, https://doi.org/10.1136/bmj.i2016. PMID: 27353417.

[14] R.T. Chlebowski, G.L. Anderson, M. Gass, D.S. Lane, A.K. Aragaki, L.H. Kuller, J. E. Manson, M.L. Stefanick, J. Ockene, G.E. Sarto, K.C. Johnson, J. Wactawski-Wende, P.M. Ravdin, R. Schenken, S.L. Hendrix, A. Rajkovic, T.E. Rohan, S. Yasmeen, R.L. Prentice, WHI Investigators, Estrogen plus progestin and BREAST CANCER incidence and mortality in postmenopausal women, JAMA. 304 (15) (2010 Oct 20) 1684–1692, https://doi.org/10.1001/jama.2010.1500.

[15] G.L. Anderson, R.T. Chlebowski, A.K. Aragaki, L.H. Kuller, J.E. Manson, M. Gass, E. Bluhm, S. Connelly, F.A. Hubbell, D. Lane, L. Martin, J. Ockene, T. Rohan, R. Schenken, J. Wactawski-Wende, Conjugated equine oestrogen and BREAST CANCER incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial, Lancet Oncol. 13 (5) (2012 May) 476–486, https://doi.org/10.1016/S1470-2045(12)70075-X.

[16] J.E. Manson, R.T. Chlebowski, M.L. Stefanick, A.K. Aragaki, J.E. Rossouw, R. L. Prentice, G. Anderson, B.V. Howard, C.A. Thomson, A.Z. LaCroix, J. Wactawski-Wende, R.D. Jackson, M. Limacher, K.L. Margolis, S. Wassertheil-Smoller, S.A. Beresford, J.A. Cauley, C.B. Eaton, M. Gass, J. Hsia, K.C. Johnson, C. Kooperberg, L.H. Kuller, C.E. Lewis, S. Liu, L.W. Martin, J.K. Ockene, M. J. O'Sullivan, L.H. Powell, M.S. Simon, L. Van Horn, M.Z. Vitolins, R.B. Wallace, Menopausal hormone therapy and health outcomes during the intervention and extended post-stopping phases of the Women's Health Initiative randomized trials, JAMA 310 (13) (2013 Oct 2) 1353–1368, https://doi.org/10.1001/jama.2013.278040.

[17] J.E. Manson, A.K. Aragaki, J.E. Rossouw, G.L. Anderson, R.L. Prentice, A. Z. LaCroix, R.T. Chlebowski, B.V. Howard, C.A. Thomson, K.L. Margolis, C. E. Lewis, M.L. Stefanick, R.D. Jackson, K.C. Johnson, L.W. Martin, S.A. Shumaker, M.A. Espeland, J. Wactawski-Wende, WHI Investigators, Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative Randomized Trials, JAMA. 318 (10) (2017 Sep 12) 927–938, https://doi.org/10.1001/jama.2017.11217.

[18] M. Nudy, V.M. Chinchilli, A.J. Foy, A systematic review and meta-regression analysis to examine the 'timing hypothesis' of hormone replacement therapy on mortality, coronary heart disease, and stroke, Int. J. Cardiol. Heart Vasc. 22 (2019 Jan 18) 123–131, https://doi.org/10.1016/j.ijcha.2019.01.001.

[19] J.E. Kim, J.H. Chang, M.J. Jeong, J. Choi, J. Park, C. Baek, A. Shin, S.M. Park, D. Kang, J.Y. Choi, A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases, Sci. Rep. 10 (1) (2020 Nov 26) 20631, https://doi.org/10.1038/s41598-020-77534-9.

[20] D. Zhu, H.F. Chung, A.J. Dobson, N. Pandeya, G.G. Giles, F. Bruinsma, E. J. Brunner, D. Kuh, R. Hardy, N.E. Avis, E.B. Gold, C.A. Derby, K.A. Matthews, J. E. Cade, D.C. Greenwood, P. Demakakos, D.E. Brown, L.L. Sievert, D. Anderson, K. Hayashi, J.S. Lee, H. Mizunuma, T. Tillin, M.K. Simonsen, H.O. Adami, E. Weiderpass, G.D. Mishra, Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data, Lancet Public Health 4 (11) (2019 Nov) e553–e564, https://doi.org/10.1016/S2468-2667(19)30155-0.

[21] Y. Vinogradova, C. Coupland, J. Hippisley-Cox, Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases, BMJ 364 (2019 Jan 9), k4810, https://doi.org/10.1136/bmj.k4810. Erratum in: BMJ. 2019 Jan 15;364:l162.

[22] T. Muka, C. Oliver-Williams, S. Kunutsor, J.S. Laven, B.C. Fauser, R. Chowdhury, M. Kavousi, O.H. Franco, Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis, JAMA Cardiol. 1 (7) (2016) 767–776, https://doi.org/10.1001/jamacardio.2016.2415.

[23] Y. Vinogradova, C. Coupland, J. Hippisley-Cox, Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases, BMJ. 371 (2020 Oct 28) m3873, https://doi.org/10.1136/bmj.m3873.

[24] Collaborative Group on Hormonal Factors in breast cancer, Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence, Lancet. 394 (10204) (2019 Sep 28) 1159–1168, https://doi.org/10.1016/S0140-6736(19)31709-X.

[25] V. Beral, K. Gaitskell, C. Hermon, K. Moser, G. Reeves, R. Peto, Collaborative Group On Epidemiological Studies Of Ovarian Cancer, Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52

epidemiological studies, Lancet. 385 (9980) (2015 May 9) 1835–1842, https://doi.org/10.1016/S0140-6736(14)61687-1.
[26] S. Sweetland, V. Beral, A. Balkwill, B. Liu, V.S. Benson, M. Canonico, J. Green, G. K. Reeves, Million Women Study Collaborators, Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study, J. Thromb. Haemost. 10 (11) (2012 Nov) 2277–2286, https://doi.org/10.1111/j.1538-7836.2012.04919.x.
[27] N. Asie, K. Mohammed, Q. Haydour, M.R. Gionfriddo, O.L. Vargas, L.J. Prokop, S. S. Faubion, M.H. Murad, Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis, Syst. Rev. 5 (1) (2016 Jul 26) 121, https://doi.org/10.1186/s13643-016-0294-5. PMID: 27456847; PMCID: PMC4960754.
[28] E. Hoibraaten, H. Arnesen, S. Larsen, E. Wickstrom, P.M. Sandset, Increased risk of recurrent venous thromboembolism during hormone replacement therapy: results of the randomized, double blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET), Thromb. Haemost. 84 (2000) 961–967.
[29] V. Olié, G. Plu-Bureau, J. Conard, M.H. Horellou, M. Canonico, P.Y. Scarabin, Hormone therapy and recurrence of venous thromboembolism among postmenopausal women, Menopause. 18 (5) (2011 May) 488–493.
[30] J.E. Rossouw, G.L. Anderson, R.L. Prentice, A.Z. LaCroix, C. Kooperberg, M. L. Stefanick, R.D. Jackson, S.A. Beresford, B.V. Howard, K.C. Johnson, J. M. Kotchen, J. Ockene, Writing Group for the Women's Health Initiative Investigators, Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial, JAMA 288 (3) (2002 Jul 17) 321–333.
[31] M. Canonico, G. Plu-Bureau, G.D. Lowe, P.Y. Scarabin, Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis, BMJ 336 (7655) (2008 May 31) 1227–1231, https://doi.org/10.1136/bmj.39555.441944.BE. Epub 2008 May 20. PMID: 18495631; PMCID: PMC2405857.
[32] T. Ohira, A.R. Folsom, M. Cushman, R.H. White, P.J. Hannan, W.D. Rosamond, S. R. Heckbert, Reproductive history, hormone replacement, and incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology, Br. J. Haematol. 149 (4) (2010 May) 606–612, https://doi.org/10.1111/j.1365-2141.2010.08128.x. Epub 2010 Mar 3. PMID: 20230397; PMCID: PMC2864348.
[33] C. Renoux, S. Dell'Aniello, S. Suissa, Hormone replacement therapy and the risk of venous thromboembolism: a population-based study, J. Thromb. Haemost. 8 (5) (2010 May) 979–986, https://doi.org/10.1111/j.1538-7836.2010.03839.x. Epub 2010 Mar 4, 20230416.
[34] D. Rovinski, R.B. Ramos, T.M. Fighera, G.K. Casanova, P.M. Spritzer, Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: a systematic review and meta-analysis, Thromb. Res. 168 (2018 Aug) 83–95, https://doi.org/10.1016/j.thromres.2018.06.014. Epub 2018 Jun 19, 29936403.
[35] D.M. Herrington, E. Vittinghoff, T.D. Howard, D.A. Major, J. Owen, D. M. Reboussin, D. Bowden, V. Bittner, J.A. Simon, D. Grady, S.B. Hulley, Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease, Arterioscler. Thromb. Vasc. Biol. 22 (6) (2002 Jun 1) 1012–1017, https://doi.org/10.1161/01.atv.0000018301.91721.94.
[36] M. Cushman, L.H. Kuller, R. Prentice, R.J. Rodabough, B.M. Psaty, R.S. Stafford, S. Sidney, F.R. Rosendaal, Women's Health Initiative Investigators, Estrogen plus progestin and risk of venous thrombosis, JAMA. 292 (13) (2004 Oct 6) 1573–1580, https://doi.org/10.1001/jama.292.13.1573. 15467059.
[37] G. Lowe, M. Woodward, M. Vessey, A. Rumley, P. Gough, E. Daly, Thrombotic variables and risk of idiopathic venous thromboembolism in women aged 45-64 years. Relationships to hormone replacement therapy, Thromb. Haemost. 83 (4) (2000 Apr) 530–535. 10780311.
[38] F.R. Rosendaal, M. Vessey, A. Rumley, E. Daly, M. Woodward, F.M. Helmerhorst, G.D. Lowe, Hormonal replacement therapy, prothrombotic mutations and the risk of venous thrombosis, Br. J. Haematol. 116 (4) (2002 Mar) 851–854, https://doi.org/10.1046/j.0007-1048.2002.03356.x. 11886391.
[39] J.D. Douketis, J.A. Julian, M.A. Crowther, C. Kearon, S.M. Bates, M. Barone, F. Piovella, S. Middeldorp, P. Prandoni, M. Johnston, L. Costantini, J.S. Ginsberg, The effect of prothrombotic blood abnormalities on risk of deep vein thrombosis in users of hormone replacement therapy: a prospective case-control study, Clin. Appl. Thromb. Hemost. 17 (6) (2011 Nov-Dec) E106–E113, https://doi.org/10.1177/1076029610387587. Epub 2010 Dec 15, 21159708.
[40] C. Straczek, E. Oger, M.B. Yon de Jonage-Canonico, G. Plu-Bureau, J. Conard, G. Meyer, M. Alhenc-Gelas, H. Lévesque, N. Trillot, M.T. Barrellier, D. Wahl, J. Emmerich, P.Y. Scarabin, Estrogen and Thromboembolism Risk (ESTHER) Study Group, Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration, Circulation 112 (22) (2005 Nov 29) 3495–3500, https://doi.org/10.1161/CIRCULATIONAHA.105.565556. Epub 2005 Nov 21, 16301339.
[41] L. Li, U.G. Schulz, W. Kuker, P.M. Rothwell, Oxford Vascular Study, Age-specific association of migraine with cryptogenic TIA and stroke: population-based study, Neurology 85 (17) (2015 Oct 27) 1444–1451, https://doi.org/10.1212/WNL.0000000000002059. Epub 2015 Sep 30, 26423431.
[42] R.E. Nappi, A. Cagnacci, F. Granella, F. Piccinini, F. Polatti, F. Facchinetti, Course of primary headaches during hormone replacement therapy, Maturitas 38 (2) (2001 Apr 20) 157–163, https://doi.org/10.1016/s0378-5122(00)00215-2. 11306204.
[43] F. Facchinetti, R.E. Nappi, A. Tirelli, F. Polatti, G. Nappi, G. Sances, Hormone supplementation differently affects migraine in postmenopausal women, Headache 42 (9) (2002 Oct) 924–929, https://doi.org/10.1046/j.1526-4610.2002.02215.x. Erratum in: Headache. 2003 Feb;43(2):172. Erratum in: Headache. 2003 Mar;43(3):310. PMID, 12390622.
[44] R.E. Nappi, G. Sances, A. Sommacal, S. Detaddei, F. Facchinetti, S. Cristina, F. Polatti, G. Nappi, Different effects of tibolone and low-dose EPT in the management of postmenopausal women with primary headaches, Menopause. 13 (5) (2006 Sep-Oct) 818–825, https://doi.org/10.1097/01.gme.0000227399.53192.f5. 16894336.
[45] Boardman HMP, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, Gabriel Sanchez R, Knight B. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst. Rev. 2015, Issue 3. Art. No.: CD002229. DOI: https://doi.org/10.1002/14651858.CD002229.pub4.
[46] P. Ouyang, J. Tardif, D. Herrington, K. Stewart, P. Thompson, M. Walsh, et al., Randomized trial of hormone therapy in women after coronary bypass surgery: evidence of differential effect of hormone therapy on angiographic progression of disease in saphenous vein grafts and native coronary arteries, Atherosclerosis 189 (2) (2006) 375–386.
[47] D.M. Herrington, D.M. Reboussin, K. Bridget Brosnihan, P.C. Sharp, S. A. Shumaker, T.E. Snyder, et al., Effects of estrogen replacement on the progression of coronary-artery atherosclerosis, N. Engl. J. Med. 343 (8) (2000) 522–529. ERA.
[48] N. Cherry, K. Gilmour, P. Hannaford, A. Heagerty, M.A. Khan, H. Kitchener, R. McNamee, M. Elstein, C. Kay, M. Seif, H. Buckley, ESPRIT team, Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial, Lancet 360 (9350) (2002 Dec 21-28) 2001–2008, https://doi.org/10.1016/s0140-6736(02)12001-0.
[49] K. Bibbins-Domingo, F. Lin, E. VittinghoK, E. Barrett-Connor, S. Hulley, D. Grady, et al., Effect of hormone therapy on mortality rates among women with heart failure and coronary artery disease, Am. J. Cardiol. 95 (2) (2005) 289–291. HERS I.
[50] J. Hsia, E.L. Alderman, J.I. Verter, W.J. Rogers, P. Thompson, B.V. Howard, et al., Women's angiographic vitamin and estrogen trial: design and methods, Control. Clin. Trials 23 (2002) 708–727. WAVE.
[51] H.N. Hodis, W.J. Mack, S.P. Azen, R.A. Lobo, D. Shoupe, P.R. Mahrer, et al., Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women, N. Engl. J. Med. 349 (6) (2003) 535–545. WELL-HART.
[52] C.M. Viscoli, L.M. Brass, W.N. Kernan, P.M. Sarrel, S. Suissa, R.I. Horwitz, A clinical trial of estrogen-replacement therapy after ischemic stroke, N. Engl. J. Med. 345 (17) (2001) 1243–1249. WEST.
[53] P. Collins, M. Flather, B. Lees, R. Mister, A. Proudler, J.C. Stevenson, WHISP (Women's Hormone Intervention Secondary Prevention Study) Pilot Study Investigators, Randomized trial of effects of continuous combined HRT on markers of lipids and coagulation in women with acute coronary syndromes: WHISP Pilot Study, Eur. Heart J. 27 (17) (2006) 2046–2053. WHISP.
[54] S.C. Clarke, J. Kelleher, H. Lloyd-Jones, M. Slack, P.M. Schofiel, A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study, BJOG 109 (9) (2002 Sep) 1056–1062, https://doi.org/10.1111/j.1471-0528.2002.01544.
[55] I.A. Berglind, M. Andersen, A. Citarella, M. Linder, A. Sundström, H. Kieler, Hormone therapy and risk of cardiovascular outcomes and mortality in women treated with statins, Menopause 22 (4) (2015 Apr) 369–376, https://doi.org/10.1097/GME.0000000000000345. PMID: 25335101; PMCID: PMC4470525.
[56] D.M. Bretler, P.R. Hansen, J. Lindhardsen, O. Ahlehoff, C. Andersson, T.B. Jensen, J. Raunsø, C. Torp-Pedersen, G.H. Gislason, Hormone replacement therapy and risk of new-onset atrial fibrillation after myocardial infarction–a nationwide cohort study, PLoS One 7 (12) (2012), e51580, https://doi.org/10.1371/journal.pone.0051580.
[57] F. Grodstein, J.E. Manson, M.J. Stampfer, Postmenopausal hormone use and secondary prevention of coronary events in the nurses' health study. a prospective, observational study, Ann. Intern. Med. 135 (2001) 1–8.
[58] Khan MA, Liu MW, Singh D, Pal A, Chio FL, Lawson D, Dean LS. Long-term (three years) effect of estrogen replacement therapy on major adverse cardiac events in postmenopausal women after intracoronary stenting. Am. J. Cardiol. 2000 Aug 1; 86(3):330-3. doi: https://doi.org/10.1016/s0002-9149(00)00926-7.
[59] K.P. Alexander, L.K. Newby, A.S. Hellkamp, R.A. Harrington, E.D. Peterson, S. Kopecky, A. Langer, P. O'Gara, C.M. O'Connor, R.N. Daly, R.M. Califf, S. Khan, V. Fuster, Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up, J. Am. Coll. Cardiol. 38 (1) (2001 Jul) 1–7, https://doi.org/10.1016/s0735-1097(01)01329-8.
[60] B.G. Angeja, M.G. Shlipak, A.S. Go, S.C. Johnston, P.D. Frederick, J.G. Canto, H. V. Barron, D. Grady, National Registry of Myocardial Infarction 3 Investigators, Hormone therapy and the risk of stroke after acute myocardial infarction in postmenopausal women, J. Am. Coll. Cardiol. 38 (5) (2001 Nov 1) 1297–1301, https://doi.org/10.1016/s0735-1097(01)01551-0. 11691498.
[61] S. Apostolakis, R.M. Sullivan, B. Olshansky, G.Y. Lip, Hormone replacement therapy and adverse outcomes in women with atrial fibrillation: an analysis from

the atrial fibrillation follow-up investigation of rhythm management trial, Stroke. 45 (10) (2014 Oct) 3076–3079.
[62] J. Lindenfeld, J.K. Ghali, H.J. Krause-Steinrauf, S. Khan, K. Adams, S. Goldman, M.A. Peberdy, C. Yancy, S. Thaneemit-Chen, R.L. Larsen, J. Young, B. Lowes, Y. D. Rosenberg, BEST Investigators, Hormone replacement therapy is associated with improved survival in women with advanced heart failure, J. Am. Coll. Cardiol. 42 (7) (2003 Oct 1) 1238–1245.
[63] N.A. Nussmeier, M.R. Marino, W.K. Vaughn, Hormone replacement therapy is associated with improved survival in women undergoing coronary artery bypass grafting, J. Thorac. Cardiovasc. Surg. 124 (6) (2002 Dec) 1225–1229.
[64] W.B. White, B. Pitt, R.A. Preston, V. Hanes, Antihypertensive effects of drospirenone with 17beta-estradiol, a novel hormone treatment in postmenopausal women with stage 1 hypertension, Circulation 112 (13) (2005 Sep 27) 1979–1984, https://doi.org/10.1161/CIRCULATIONAHA.104.501502.
[65] W.B. White, V. Hanes, V. Chauhan, B. Pitt, Effects of a new hormone therapy, drospirenone and 17-beta-estradiol, in postmenopausal women with hypertension, Hypertension. 48 (2) (2006 Aug) 246–253, https://doi.org/10.1161/01.HYP.0000232179.60442.84.
[66] R.A. Preston, A. Alonso, D. Panzitta, P. Zhang, A.H. Karara, Additive effect of drospirenone/17-beta-estradiol in hypertensive postmenopausal women receiving enalapril, Am. J. Hypertens. 15 (9) (2002 Sep) 816–822, https://doi.org/10.1016/s0895-7061(02)02980-1.
[67] R.A. Preston, W.B. White, B. Pitt, G. Bakris, P.M. Norris, V. Hanes, Effects of drospirenone/17-beta estradiol on BP and potassium balance in hypertensive postmenopausal women, Am. J. Hypertens. 18 (6) (2005 Jun) 797–804, https://doi.org/10.1016/j.amjhyper.2004.12.003.
[68] R.A. Preston, P.M. Norris, A.B. Alonso, P. Ni, V. Hanes, A.H. Karara, Randomized, placebo-controlled trial of the effects of drospirenone-estradiol on BP and potassium balance in hypertensive postmenopausal women receiving hydrochlorothiazide, Menopause 14 (3 Pt 1) (2007 May-Jun) 408–414, https://doi.org/10.1097/01.gme.0000243572.63322.f7.
[69] C. Kaya, S.D. Cengiz, B. Cengiz, G. Akgun, Long-term effects of low-dose 17beta-estradiol plus dydrogesterone on 24-h ambulatory BP in healthy postmenopausal women: a 1-year, randomized, prospective study, Gynecol. Endocrinol. 23 (Suppl. 1) (2007 Oct) 62–67, https://doi.org/10.1080/09513590701584956.
[70] H. Sumino, S. Ichikawa, H. Kumakura, Y. Takayama, T. Kanda, T. Sakamaki, M. Kurabayashi, Effects of hormone replacement therapy on office and ambulatory BP in Japanese hypertensive postmenopausal women, Hypertens. Res. 26 (5) (2003 May) 369–376, https://doi.org/10.1291/hypres.26.369.
[71] M.G. Modena, R. Molinari, N. Muia Jr., A. Castelli, F. Pala, R. Rossi, Double-blind randomized placebo-controlled study of transdermal estrogen replacement therapy on hypertensive postmenopausal women, Am. J. Hypertens. 12 (10 Pt 1) (1999 Oct) 1000–1008, https://doi.org/10.1016/s0895-7061(99)00074-6.
[72] K. Kawecka-Jaszcz, D. Czarnecka, A. Olszanecka, M. Rajzer, P. Jankowski, The effect of hormone replacement therapy on arterial BP and vascular compliance in postmenopausal women with arterial hypertension, J. Hum. Hypertens. 16 (7) (2002 Jul) 509–516, https://doi.org/10.1038/sj.jhh.1001431.
[73] M.N. de Carvalho, F. Nobre, M.C. Mendes, R.M. Dos Reis, R.A. Ferriani, M.F. Silva de Sá, Low-dose transdermal hormone therapy does not interfere with the BP of hypertensive menopausal women: a pilot study, Blood Press Monit. 13 (5) (2008 Oct) 277–283, https://doi.org/10.1097/MBP.0b013e32830d4b60.
[74] G. Lloyd, E. McGing, A. Cooper, N. Patel, P.J. Lumb, A.S. Wierzbicki, G. Jackson, A randomised placebo controlled trial of the effects of tibolone on BP and lipids in hypertensive women, J. Hum. Hypertens. 14 (2) (2000 Feb) 99–104, https://doi.org/10.1038/sj.jhh.1000938.
[75] B. Andersson, L.A. Mattsson, L. Hahn, P. Mårin, L. Lapidus, G. Holm, B. A. Bengtsson, P. Björntorp, Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin-dependent diabetes mellitus, J. Clin. Endocrinol. Metab. 82 (2) (1997 Feb) 638–643.
[76] D.A. Araujo, M.L. Farias, A.T. Andrade, Effects of transdermal and oral estrogen replacement on lipids and glucose metabolism in postmenopausal women with type 2 diabetes mellitus, Climacteric. 5 (3) (2002) 286–292.
[77] H.E. Brussaard, J.A. Gevers Leuven, M. Frölich, C. Kluft, H.M. Krans, Short-term oestrogen replacement therapy improves insulin resistance, lipids and fibrinolysis in postmenopausal women with NIDDM, Diabetologia 40 (7) (1997) 843–849, https://doi.org/10.1007/s001250050758.
[78] C. Cornu, C. Mercier, P. Ffrench, et al., Postmenopause hormone treatment in women with NIDDM or impaired glucose tolerance: the MEDIA randomized clinical trial, Maturitas 37 (2) (2000) 95–104, https://doi.org/10.1016/s0378-5122(00)00164-x.
[79] D.A. Darko, A. Dornhorst, G. Kennedy, R.C. Mandeno, M. Seed, Glycaemic control and plasma lipoproteins in menopausal women with Type 2 diabetes treated with oral and transdermal combined hormone replacement therapy, Diabetes Res. Clin. Pract. 54 (3) (2000) 157–164. Xllth International Symposium on Atherosclerosis, Stockholm, Sweden, June 25-29, 2000, https://doi.org/10.1016/S0168-8227(01)00297-2.
[80] K.E. Friday, C. Dong, R.U. Fontenot, Conjugated equine estrogen improves glycemic control and blood lipoproteins in postmenopausal women with type 2 diabetes, J. Clin. Endocrinol. Metab. 86 (1) (2001) 48–52, https://doi.org/10.1210/jcem.86.1.7094.
[81] B.V. Howard, Postmenopausal hormone therapy is associated with atherosclerosis progression in women with abnormal glucose tolerance, Circulation 110 (2) (2004 Jul 13) 201–206.
[82] A.M. Kanaya, D. Herrington, E. Vittinghoff, F. Lin, D. Grady, V. Bittner, et al., Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial, Ann. Intern. Med. 138 (2003) 1e9.
[83] A.F. Kernohan, N. Sattar, T. Hilditch, S.J. Cleland, M. Small, M.A. Lumsden, et al., Effects of low-dose continuous combined hormone replacement therapy on glucose homeostasis and markers of cardiovascular risk in women with type 2 diabetes, Clin. Endocrinol. 66 (2007) 27e34.
[84] S. Lamon-Fava, D.M. Herrington, K.V. Horvath, E.J. Schaefer, B.F. Asztalos, Effect of hormone replacement therapy on plasma lipoprotein levels and coronary atherosclerosis progression in postmenopausal women according to type 2 diabetes mellitus status, Metabolism 59 (2010) 1794e800.
[85] P.J. Manning, A. Allum, S. Jones, W.H. Sutherland, S.M. Williams, The effect of hormone replacement therapy on cardiovascular risk factors in type 2 diabetes: a randomized controlled trial, Arch. Intern. Med. 161 (14) (2001) 1772–1776, https://doi.org/10.1001/archinte.161.14.1772.
[86] J. McKenzie, A.J. Jaap, S. Gallacher, A. Kelly, L. Crawford, I.A. Greer, et al., Metabolic, inflammatory and haemostatic effects of a low-dose continuous combined HRT in women with type 2 diabetes: potentially safer with respect to vascular risk? Clin. Endocrinol. 59 (2003) 682e9.
[87] H. Mosnier-Pudar, B. Faguer, T.T. Guyenne, G. Tchobroutsky, Effets de la substitution par 17 beta estradiol percutané et progestérone orale sur la pression artérielle et les paramètres métaboliques chez des patientes ménopausées diabétiques non insulinodépendantes [Effects of deprivation and replacement by percutaneous 17 beta estradiol and oral progesterone on blood pressure and metabolic parameters in menopause patients with non-insulin-dependent diabetes], Arch. Mal. Coeur Vaiss. 84 (8) (1991) 1111–1115.
[88] M. Perera, N. Sattar, J.R. Petrie, et al., The effects of transdermal estradiol in combination with oral norethisterone on lipoproteins, coagulation, and endothelial markers in postmenopausal women with type 2 diabetes: a randomized, placebo-controlled study, J. Clin. Endocrinol. Metab. 86 (3) (2001) 1140–1143, https://doi.org/10.1210/jcem.86.3.7297.
[89] K. Samaras, C.S. Hayward, D. Sullivan, R.P. Kelly, L.V. Campbell, Effects of postmenopausal hormone replacement therapy on central abdominal fat, glycemic control, lipid metabolism, and vascular factors in type 2 diabetes: a prospective study, Diabetes Care 22 (9) (1999) 1401–1407, https://doi.org/10.2337/diacare.22.9.1401.
[90] M.A. Sánchez-Rodríguez, M. Zacarías-Flores, L. Castrejón-Delgado, A.K. Ruiz-Rodríguez, V.M. Mendoza-Núñez, Effects of hormone therapy on oxidative stress in postmenopausal women with metabolic syndrome, Int. J. Mol. Sci. 17 (9) (2016 Aug 24) 1388, https://doi.org/10.3390/ijms17091388. PMID: 27563883; PMCID: PMC5037668.
[91] A.R. Scott, P. Dhindsa, J. Forsyth, P. Mansell, Effect of hormone replacement therapy on cardiovascular risk factors in postmenopausal women with diabetes, Diabetes. Obes. Metab. 6 (2004) 16–22.
[92] H. Sumino, Hormone replacement therapy decreases insulin resistance and lipid metabolism in Japanese postmenopausal women with impaired and normal glucose tolerance, Horm. Res. 60 (3) (2003) 134–142.
[93] W.H. Sutherland, P.J. Manning, S.A. de Jong, A.R. Allum, S.D. Jones, S. M. Williams, Hormone-replacement therapy increases sèrum paraoxonase arylesterase activity in diabetic postmenopausal women, Metabolism 50 (2001) 319e24.
[94] L. Thunell, B. Andersson, M. Glassell, L.A. Mattsson, The effect of continuous combined HRT on glucose homeostasis and plasma lipids. A placebo-controlled study in postmenopausal women with type 2 diabetes, Maturitas 53 (2006) 430e8.
[95] W. Xue, Y. Deng, Y.F. Wang, A.J. Sun, Effect of half-dose and standard-dose conjugated equine estrogens combined with natural progesterone or dydrogesterone on components of metabolic syndrome in healthy postmenopausal women: a Randomized Controlled Trial, Chin. Med. J. 129 (23) (2016 Dec 5) 2773–2779, https://doi.org/10.4103/0366-6999.194646. PMID: 27900987; PMCID: PMC5146781.
[96] P. Manwaring, L. Morfis, T. Diamond, L.G. Howes, The effects of hormone replacement therapy on plasma lipids in type II diabetes, Maturitas 34 (3) (2000 Mar 31) 239–247, https://doi.org/10.1016/s0378- 5122(99)00112-7. 10717490.
[97] A. Ferrara, A.J. Karter, L.M. Ackerson, J.Y. Liu, J.V. Selby, Northern California Kaiser Permanente Diabetes Registry, Hormone replacement therapy is associated with better glycemic control in women with type 2 diabetes: the Northern California Kaiser Permanente Diabetes Registry, Diabetes Care 24 (7) (2001) 1144–1150.
[98] A. Ferrara, Current use of unopposed estrogen and estrogen plus progestin and the risk of acute myocardial infarction among women with diabetes: the Northern California Kaiser Permanent Diabetes Registry, 1995-8, Circulation. 107 (1) (2003 Jan 7) 43–48.
[99] J.E. Kim, J. Choi, J. Park, J.K. Lee, A. Shin, S.M. Park, D. Kang, J.Y. Choi, Associations of postmenopausal hormone therapy with metabolic syndrome among diabetic and non-diabetic women, Maturitas. 121 (2019 Mar) 76–82, https://doi.org/10.1016/j.maturitas.2018.12.012. Epub 2018 Dec 20, 30704569.

[100] K.M. Newton, A.Z. LaCroix, S.R. Heckbert, L. Abraham, D. McCulloch, W. Barlow, Estrogen therapy and risk of cardiovascular events among women with type 2 diabetes, Diabetes Care 26 (10) (2003) 2810–2816, https://doi.org/10.2337/diacare.26.10.2810.
[101] A.S. Gami, R.S. Wright, K.V. Ballman, S.L. Kopecky, S.N. Hayes, Hormone replacement therapy and risk of acute myocardial infarction in postmenopausal women with diabetes mellitus, Am. J. Cardiol. 91 (10) (2003) 1275–1277, https://doi.org/10.1016/s0002-9149(03)00284-4.
[102] C.J. Crespo, E. Smit, A. Snelling, C.T. Sempos, R.E. Andersen, NHANES III, Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III), Diabetes Care 25 (10) (2002 Oct) 1675–1680, https://doi.org/10.2337/diacare.25.10.1675.
[103] C.K. Sites, M. Brochu, A. Tchernof, E.T. Poehlman, Relationship between hormone replacement therapy use with body fat distribution and insulin sensitivity in obese postmenopausal women, Metabolism. 50 (7) (2001) 835–840.
[104] M.A. Osmanağaoğlu, S. Osmanağaoğlu, T. Osmanağaoğlu, B. Okumuş, H. Bozkaya, Effect of different preparations of hormone therapy on lipid and glucose metabolism, coagulation factors, and bone mineral density in overweight and obese postmenopausal women, Fertil. Steril. 84 (2) (2005) 384–393.
[105] M. Canonico, E. Oger, J. Conard, G. Meyer, H. Lévesque, N. Trillot, M. T. Barrellier, D. Wahl, J. Emmerich, P.Y. Scarabin, EStrogen and THromboEmbolism Risk (ESTHER) Study Group, Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study, J. Thromb. Haemost. 4 (6) (2006 Jun) 1259–1265, https://doi.org/10.1111/j.1538-7836.2006.01933.x.
[106] S.V. Kane, Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease, Am. J. Gastroenterol. 103 (5) (2008 May) 1193–1196.
[107] V. Di Martino, Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure, Hepatology. 40 (6) (2004 Dec) 1426–1433.
[108] L. Codes, T. Asselah, D. Cazals-Hatem, F. Tubach, D. Vidaud, R. Paraná, P. Bedossa, D. Valla, P. Marcellin, Liver fibrosis in women with chronic hepatitis C: evidence for the negative role of the menopause and steatosis and the potential benefit of hormone replacement therapy, Gut. 56 (3) (2007 Mar) 390–395, https://doi.org/10.1136/gut.2006.101931.
[109] M. Rinaldi, A. Cagnacci, F.E. Pansini, D. de Aloysio, M.P. Sgarabotto, A. Bacchi-Modena, Neutral effect of prolonged transdermal hormone therapy on liver function of postmenopausal women with chronic active hepatitis, Menopause. 12 (5) (2005 Sep-Oct) 619–622.
[110] E. von Schoultz, L.E. Rutqvist, Stockholm Breast Cancer Study Group, Menopausal hormone therapy after breast cancer: the Stockholm randomized trial, J. Natl. Cancer Inst. 97 (7) (2005 Apr 6) 533–535.
[111] M. Fahlén, T. Fornander, H. Johansson, U. Johansson, L.E. Rutqvist, N. Wilking, E. von Schoultz, Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial, Eur. J. Cancer 49 (1) (2013 Jan) 52–59, https://doi.org/10.1016/j.ejca.2012.07.003.
[112] L. Holmberg, H. Anderson, HABITS steering and data monitoring committees, HABITS (hormonal replacement therapy after breast cancer–is it safe?), a randomised comparison: trial stopped, Lancet. 363 (9407) (2004 Feb 7) 453–455.
[113] L. Holmberg, O.E. Iversen, C.M. Rudenstam, M. Hammar, E. Kumpulainen, J. Jaskiewicz, J. Jassem, D. Dobaczewska, H.E. Fjosne, O. Peralta, R. Arriagada, M. Holmqvist, J. Maenpaa, HABITS Study Group, Increased risk of recurrence after hormone replacement therapy in breast cancer survivors, J. Natl. Cancer Inst. 100 (7) (2008 Apr 2) 475–482, https://doi.org/10.1093/jnci/djn058.
[114] M.B. Marttunen, P. Hietanen, S. Pyrhönen, A. Tiitinen, O. Ylikorkala, A prospective study on women with a history of breast cancer and with or without estrogen replacement therapy, Maturitas. 39 (3) (2001 Sep 28) 217–225.
[115] D.A. Decker, J.E. Pettinga, N. VanderVelde, R.R. Huang, L. Kestin, J.H. Burdakin, Estrogen replacement therapy in breast cancer survivors: a matched-controlled series, Menopause. 10 (4) (2003 Jul-Aug) 277–285.
[116] R. Vassilopoulou-Sellin, D.S. Cohen, G.N. Hortobagyi, M.J. Klein, M. McNeese, S. E. Singletary, T.L. Smith, R.L. Theriault, Estrogen replacement therapy for menopausal women with a history of breast carcinoma: results of a 5-year, prospective study, Cancer. 95 (9) (2002 Nov 1) 1817–1826.
[117] E.M. Durna, B.G. Wren, G.Z. Heller, L.R. Leader, P. Sjoblom, J.A. Eden, Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality, Med. J. Aust. 177 (7) (2002 Oct 7) 347–351.
[118] M.W. Beckmann, D. Jap, S. Djahansouzi, C. Nestle-Krämling, B. Kuschel, P. Dall, C. Brumm, H.G. Bender, Hormone replacement therapy after treatment of breast cancer: effects on postmenopausal symptoms, bone mineral density and recurrence rates, Oncology. 60 (3) (2001) 199–206.
[119] E.S. O'Meara, M.A. Rossing, J.R. Daling, J.G. Elmore, W.E. Barlow, N.S. Weiss, Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality, J. Natl. Cancer Inst. 93 (10) (2001 May 16) 754–762.
[120] P. Kenemans, N.J. Bundred, J.M. Foidart, E. Kubista, B. von Schoultz, P. Sismondi, R. Vassilopoulou-Sellin, C.H. Yip, J. Egberts, M. Mol-Arts, R. Mulder, S. van Os, M. W. Beckmann, LIBERATE Study Group, Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial, Lancet Oncol. 10 (2) (2009 Feb) 135–146, https://doi.org/10.1016/S1470- 2045(08)70341-3.
[121] P.J. DiSaia, W.R. Brewster, A. Ziogas, H. Anton-Culver, Breast cancer survival and hormone replacement therapy: a cohort analysis, Am. J. Clin. Oncol. 23 (6) (2000 Dec) 541–545.
[122] P.J. DiSaia, E.A. Grosen, T. Kurosaki, M. Gildea, B. Cowan, H. Anton-Culver, Hormone replacement therapy in breast cancer survivors: a cohort study, Am. J. Obstet. Gynecol. 174 (5) (1996 May) 1494–1498.
[123] B. Cai, J. Simon, P. Villa, N. Biglia, N. Panay, S. Djumaeva, M. Particco, H. Kanakamedala, C. Altomare, No increase in incidence or risk of recurrence of breast cancer in ospemifene-treated patients with vulvovaginal atrophy (VVA), Maturitas. 142 (2020 Dec) 38–44.
[124] A. Eisen, J. Lubinski, J. Gronwald, P. Moller, H.T. Lynch, J. Klijn, C. Kim-Sing, S. L. Neuhausen, L. Gilbert, P. Ghadirian, S. Manoukian, G. Rennert, E. Friedman, C. Isaacs, E. Rosen, B. Rosen, M. Daly, P. Sun, S.A. Narod, Hereditary Breast Cancer Clinical Study Group, Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers, J. Natl. Cancer Inst. 100 (19) (2008 Oct 1) 1361–1367, https://doi.org/10.1093/jnci/djn313.
[125] J. Kotsopoulos, T. Huzarski, J. Gronwald, P. Moller, H.T. Lynch, S.L. Neuhausen, L. Senter, R. Demsky, W.D. Foulkes, C. Eng, B. Karlan, N. Tung, C.F. Singer, P. Sun, J. Lubinski, S.A. Narod, Hormone replacement therapy after menopause and risk of breast cancer in BRCA1 mutation carriers: a case-control study, Breast Cancer Res. Treat. 155 (2) (2016 Jan) 365–373, https://doi.org/10.1007/s10549-016-3685-3. Epub 2016 Jan 16, 26780555.
[126] T.R. Rebbeck, T. Friebel, T. Wagner, H.T. Lynch, J.E. Garber, M.B. Daly, C. Isaacs, O.I. Olopade, S.L. Neuhausen, L. van't Veer, R. Eeles, D.G. Evans, G. Tomlinson, E. Matloff, S.A. Narod, A. Eisen, S. Domchek, K. Armstrong, B.L. Weber, PROSE Study Group, Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group, J. Clin. Oncol. 23 (31) (2005 Nov 1) 7804–7810, https://doi.org/10.1200/JCO.2004.00.8151. Epub 2005 Oct 11. PMID: 16219936.
[127] J. Kotsopoulos, J. Gronwald, B.Y. Karlan, T. Huzarski, N. Tung, P. Moller, S. Armel, H.T. Lynch, L. Senter, A. Eisen, C.F. Singer, W.D. Foulkes, M. R. Jacobson, P. Sun, J. Lubinski, S.A. Narod, Hereditary Breast Cancer Clinical Study Group, Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers, JAMA Oncol. 4 (8) (2018 Aug 1) 1059–1065, https://doi.org/10.1001/jamaoncol.2018.0211.
[128] R.A. Eeles, J.P. Morden, M. Gore, J. Mansi, J. Glees, M. Wenxzl, et al., Adjuvant hormone therapy may improve survival in epithelial ovarian cancer: results of the AHT Randomized Trial, J. Clin. Oncol. 33 (35) (2015) 4138–4144, https://doi.org/10.1200/JCO.2015.60.9719.
[129] L. Li, Z. Pan, K. Gao, W. Zhang, Y. Luo, Z. Yao, et al., Impact of postoperative hormone replacement therapy on life quality and prognosis in patients with ovarian malignancy, Oncol. Lett. 3 (1) (2012) 244–249.
[130] F. Guidozzi, A. Daponte, Estrogen replacement therapy for ovarian carcinoma survivors: a randomized controlled trial, Cancer 86 (6) (1999) 1013–1018.
[131] R.A. Eeles, S. Tan, E. Wiltshaw, et al., Hormone replacement therapy and survival after surgery for ovarian cancer, BMJ 302 (1991) 259–262.
[132] M. Ursic-Vrscaj, S. Bebar, M.P. Zakelj, Hormone replacement therapy after invasive ovarian serous cystadenocarcinoma treatment: the effect on survival, Menopause 8 (2001) 70–75.
[133] C. Mascarenhas, M. Lambe, R. Bellocco, et al., Use of hormone replacement therapy before and after ovarian cancer diagnosis and ovarian cancer survival, Int. J. Cancer 119 (2006) 2907–2915.
[134] Y. Wen, H. Huang, H. Huang, M. Wu, K. Shen, L. Pan, The safety of postoperative hormone replacement therapy in epithelial ovarian cancer patients in China, Climacteric 16 (2013) 673–681.
[135] L. Power, G. Lefas, P. Lambert, D. Kim, D. Evaniuk, R. Lotocki, E. Dean, M. W. Nachtigal, A.D. Altman, Hormone use after nonserous epithelial ovarian cancer: overall and disease-free survival, Obstet. Gynecol. 127 (5) (2016 May) 837–847.
[136] Y.L. Zhang, J.H. Chen, W. Lu, B.L. Li, Q.Y. Zhu, X.P. Wan, Efficacy of post-operative hormone replacement therapy on prognosis of patients with serous ovarian carcinoma, Chin. Med. J. 129 (11) (2016 Jun 5) 1316–1321.
[137] R.R. Barakat, B.N. Bundy, N.M. Spirtos, J. Bell, R.S. Mannel, Gynecologic Oncology Group Study, Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study, J. Clin. Oncol. 24 (4) (2006) 587–592.
[138] A. Ayhan, C. Taskiran, S. Simsek, A. Sever, Does immediate hormone replacement therapy affect the oncologic outcome in endometrial cancer survivors? Int. J. Gynecol. Cancer 16 (2006) 805–808.
[139] K.A. Suriano, M. McHale, C.E. McLaren, K.T. Li, A. Re, P.J. DiSaia, Estrogen replacement therapy in endometrial cancer patients: a matched control study, Obstet. Gynecol. 97 (2001) 555–560.
[140] A.C. Arteaga-Gómez, G. Castellanos-Barroso, A. Colin-Valenzuela, J. García-Vargas, G. Márquez-Acosta, E. Reyes-Muñoz, Hormone therapy effect in post-menopausal women with history of endometrial cancer, Ginecol. Obstet. Mex. 79 (1) (2011 Jan) 11–17.
[141] W.T. Creasman, D. Henderson, W. Hinshaw, D.L. Clarke-Pearson, Estrogen replacement therapy in the patient treated for endometrial cancer, Obstet. Gynecol. 67 (1986) 326–330.
[142] R.B. Lee, T.W. Burke, R.C. Park, Estrogen replacement therapy following treatment for stage I endometrial carcinoma, Gynecol. Oncol. 36 (1990) 189–191.

[143] J.A. Chapman, P.J. DiSaia, K. Osann, P.D. Roth, D.L. Gillotte, M.L. Berman, Estrogen replacement in surgical stage I and II endometrial cancer survivors, Am. J. Obstet. Gynecol. 175 (1996) 1195–1200.
[144] S. Lim, Y.H. Kim, K.B. Lee, J.M. Lee, The influence of hormone therapy with drospirenone-estradiol on endometrioid type endometrial cancer patients, J. Gynecol. Oncol. 29 (5) (2018 Sep), e72, https://doi.org/10.3802/jgo.2018.29.e72.
[145] H.W. Cho, Y.T. Ouh, J.K. Lee, J.H. Hong, Effects of hormone therapy on recurrence in endometrial cancer survivors: a nationwide study using the Korean Health Insurance Review and Assessment Service database, J. Gynecol. Oncol. 30 (4) (2019 Jul), e51, https://doi.org/10.3802/jgo.2019.30.e51.
[146] E. Ploch, Hormone replacement therapy in patients after cervical cancer treatment, Gynecol. Oncol. 26 (1987) 169–177.
[147] J.A. Chan, J.A. Meyerhardt, A.T. Chan, E.L. Giovannucci, G.A. Colditz, C.S. Fuchs, Hormone replacement therapy and survival after colorectal cancer diagnosis, J. Clin. Oncol. 24 (36) (2006) 5680–5686.
[148] H. Arem, Y. Park, A.S. Felix, A. Zervoudakis, L.A. Brinton, C.E. Matthews, M. J. Gunter, Reproductive and hormonal factors and mortality among women with colorectal cancer in the NIH-AARP Diet and Health Study, Br. J. Cancer 113 (3) (2015) 562–568.
[149] M.T. Mandelson, D. Miglioretti, P.A. Newcomb, R. Harrison, J.D. Potter, Hormone replacement therapy in relation to survival in women diagnosed with colon cancer, Cancer Causes Control 14 (10) (2003) 979–984.
[150] J. Ji, J. Sundquist, K. Sundquist, Use of hormone replacement therapy improves the prognosis in patients with colorectal cancer: a population-based study in Sweden, Int. J. Cancer 142 (10) (2018) 2003–2010.
[151] M.L. Slattery, K. Anderson, W. Samowitz, S.L. Edwards, K. Curtin, B. Caan, J. D. Potter, Hormone replacement therapy and improved survival among postmenopausal women diagnosed with colon cancer (USA), Cancer Causes Control 10 (5) (1999) 467–473.
[152] A.K. Ganti, A.E. Sahmoun, A.W. Panwalkar, et al., Hormone replacement therapy is associated with decreased survival in women with lung cancer[J], J. Clin. Oncol. 24 (1) (2006) 59–63.
[153] O. Ayeni, A. Robinson, Hormone replacement therapy and outcomes for women with non-small-cell lung cancer: can an association be confirmed? Curr. Oncol. 16 (3) (2009) 21–25.
[154] H. Katcoff, A.S. Wenzlaff, A.G. Schwartz, Survival in women with NSCLC: the role of reproductive history and hormone use, J. Thorac. Oncol. 9 (3) (2014) 355–361.
[155] B. Huang, H. Carloss, S.W. Wyatt, et al., Hormone replacement therapy and survival in lung cancer in postmenopausal women in a rural population, Cancer 115 (18) (2009) 4167–4175.
[156] J. Clague, P. Reynolds, K.D. Henderson, J. Sullivan-Halley, H. Ma, J.V. Lacey Jr., S. Chang, G.L. Delclos, X.L. Du, M.R. Forman, L. Bernstein, Menopausal hormone therapy and lung cancer-specific mortality following diagnosis: the California Teachers Study, PLoS One 9 (7) (2014), e103735.
[157] K. Li, L. Chen, Y. Huang, X. Luan, Meta-analysis for the effect of hormone replacement therapy on survival rate in female with lung cancer, Zhong Nan Da Xue Bao Yi Xue Ban 45 (4) (2020) 372–377.
[158] R.M. MacKie, C.A. Bray, Hormone replacement therapy after surgery for stage 1 or 2 cutaneous melanoma, Br. J. Cancer 90 (4) (2004) 770–772.
[159] A.M. Malek, C.J. Vladutiu, M.L. Meyer, M. Cushman, R. Newman, L.D. Lisabeth, D. Kleindorfer, S. Lakkur, V.J. Howard, The association of age at menopause and all-cause and cause-specific mortality by race, postmenopausal hormone use, and smoking status, Prev. Med. Rep. 15 (2019) 100955, https://doi.org/10.1016/j.pmedr.2019.100955.
[160] P.W. Wilson, R.J. Garrison, W.P. Castelli, Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study, N. Engl. J. Med. 313 (17) (1985) 1038–1043, https://doi.org/10.1056/NEJM198510243131702.
[161] R.D. Mann, Y. Lis, J. Chukwujindu, D.O. Chanter, A study of the association between hormone replacement therapy, smoking and the occurrence of myocardial infarction in women, J. Clin. Epidemiol. 47 (3) (1994) 307–312, https://doi.org/10.1016/0895-4356(94)90014-0.
[162] A.O. Mueck, H. Seeger, Smoking, estradiol metabolism and hormone replacement therapy, Arzneimittelforschung. 53 (1) (2003) 1–11, https://doi.org/10.1055/s-0031-1297063. 12608008.
[163] A.O. Mueck, H. Seeger, Smoking, estradiol metabolism and hormone replacement therapy, Curr. Med. Chem. Cardiovasc. Hematol. Agents 3 (1) (2005 Jan) 45–54, https://doi.org/10.2174/1568016052773270. 15638743.
[164] L. Driul, A. Stella, D. Marchesoni, Twenty-four hour ambulatory blood pressure in postmenopausal smokers and non-smokers on hormone therapy, Int. J. Gynecol. Obstet. 90 (2005) 82–83.
[165] J. Geisler, I.H. Omsjø, S.I. Helle, D. Ekse, T. Silsand, P.E. Lønning, Plasma oestrogen fractions in postmenopausal women receiving hormone replacement therapy: influence of route of administration and cigarette smoking, J. Endocrinol. 162 (2) (1999) 265–270, https://doi.org/10.1677/joe.0.1620265.
[166] D.R. Abernethy, E.L. Todd, Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives, Eur. J. Clin. Pharmacol. 28 (1985) 425–428.
[167] D.R. Abernethy, D.J. Greenblatt, R.I. Shader, Imipramine disposition in users of oral contraceptive steroids, Clin. Pharmacol. Ther. 35 (6) (1984 Jun) 792–797.
[168] D.R. Abernethy, D.J. Greenblatt, M. Divoll, R. Arendt, H.R. Ochs, R.I. Shader, Impairment of diazepam metabolism by low-dose estrogen-containing oral-contraceptive steroids, N. Engl. J. Med. 306 (13) (1982 Apr 1) 791–792.
[169] S.L. Altschuler, J.W. Valenteen, Amenorrhea following rifampin administration during oral contraceptive use, Obstet. Gynecol. 44 (5) (1974 Nov) 771–772.
[170] E. Andrews, B.D. Damle, A. Fang, G. Foster, P. Crownover, R. LaBadie, P. Glue, Pharmacokinetics and tolerability of voriconazole and a combination oral contraceptive co-administered in healthy female subjects, Br. J. Clin. Pharmacol. 65 (4) (2008) 531–539.
[171] D.J. Back, A.M. Breckenridge, F. Crawford, M. MacIver, M.L. Orme, B.K. Park, P. H. Rowe, E. Smith, The effect of rifampicin on norethisterone pharmacokinetics, Eur. J. Clin. Pharmacol. 15 (3) (1979 Apr 17) 193–197.
[172] D.J. Back, A.M. Breckenridge, F.E. Crawford, J.M. Hall, M. MacIver, M.L. Orme, P. H. Rowe, E. Smith, M.J. Watts, The effect of rifampicin on the pharmacokinetics of ethynylestradiol in women, Contraception. 21 (2) (1980 Feb) 135–143.
[173] O. Baisini, F. Benini, F. Petraglia, W. Kuhnz, S. Scalia, H.U. Marschall, G. Brunetti, H.D. Tauschel, A. Lanzini, Ursodeoxycholic acid does not affect ethinylestradiol bioavailability in women taking oral contraceptives, Eur. J. Clin. Pharmacol. 60 (7) (2004 Sep) 481–487.
[174] P. Barditch-Crovo, C.B. Trapnell, E. Ette, H.A. Zacur, J. Coresh, L.E. Rocco, C. W. Hendrix, C. Flexner, The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive, Clin. Pharmacol. Ther. 65 (4) (1999 Apr) 428–438.
[175] J.C. Bessot, R. Petitjean, A. Vandevenne, M. Rempp, G. Burghard, Rifampicin interference with oral contraceptives, J. Med. Strasb. 8 (3) (1977 Mar) 131–133.
[176] H. Blode, S. Zeun, S. Parke, T. Zimmermann, B. Rohde, U. Mellinger, M. Kunz, Evaluation of the effects of rifampicin, ketoconazole and erythromycin on the steady-state pharmacokinetics of the components of a novel oral contraceptive containing estradiol valerate and dienogest in healthy postmenopausal women, Contraception. 86 (2012) 337–344.
[177] H.M. Bolt, M. Bolt, H. Kappus, Interaction of rifampicin treatment with pharmacokinetics and metabolism of ethinyloestradiol in man, Acta Endocrinol. 85 (1) (1977 May) 189–197.
[178] H.M. Bolt, H. Kappus, M. Bolt, Effect of rifampicin treatment on the metabolism of oestradiol and 17alpha-ethinyloestradiol by human liver microsomes, Eur. J. Clin. Pharmacol. 8 (5) (1975 Jun 13) 301–307.
[179] A.M. Breckenridge, D.J. Back, M. Orme, Interactions between oral contraceptives and other drugs, Pharmacol. Ther. 7 (3) (1979) 617–626.
[180] R.D. Christen, E.F. McClay, S.C. Plaxe, S.S. Yen, S. Kim, S. Kirmani, L.L. Wilgus, D. D. Heath, D.R. Shalinsky, J.L. Freddo, et al., Phase I/pharmacokinetic study of high-dose progesterone and doxorubicin, J. Clin. Oncol. 11 (12) (1993 Dec) 2417–2426.
[181] F. Cotton, P. Sorlin, B. Corvilain, J.M. Fockedey, P. Capel, Interference with oral anticoagulant treatment by oestrogen–influence of oestrogen administration route, Thromb. Haemost. 81 (3) (1999 Mar) 471–472.
[182] C.B. Coulam, J.F. Annegers, Do anticonvulsants reduce the efficacy of oral contraceptives? Epilepsia. 20 (5) (1979 Oct) 519–525.
[183] P. Crawford, D. Chadwick, P. Cleland, J. Tjia, A. Cowie, D.J. Back, M.L. Orme, The lack of effect of sodium valproate on the pharmacokinetics of oral contraceptive steroids, Contraception. 33 (1) (1986 Jan) 23–29.
[184] E. de Teresa, A. Vera, J. Ortigosa, L.A. Pulpon, A.P. Arus, M. de Artaza, Interaction between anticoagulants and contraceptives: an unsuspected finding, Br. Med. J. 2 (6200) (1979 Nov 17) 1260–1261.
[185] A. Decensi, S. Gandini, D. Serrano, M. Cazzaniga, M. Pizzamiglio, F. Maffini, G. Pelosi, C. Daldoss, U. Omodei, H. Johansson, D. Macis, M. Lazzeroni, M. Penotti, L. Sironi, S. Moroni, V. Bianco, G. Rondanina, J. Gjerde, A. Guerrieri-Gonzaga, B. Bonanni, Randomized dose-ranging trial of tamoxifen at low doses in hormone replacement therapy users, J. Clin. Oncol. 25 (27) (2007 Sep 20) 4201–4209.
[186] J.E. Dew, B.G. Wren, J.A. Eden, Tamoxifen, hormone receptors and hormone replacement therapy in women previously treated for breast cancer: a cohort study, Climacteric. 5 (2) (2002 Jun) 151–155.
[187] M.P. Diamond, J.W. Greene, J.M. Thompson, J.E. VanHooydonk, A.C. Wentz, Interaction of anticonvulsants and oral contraceptives in epileptic adolescents, Contraception. 31 (6) (1985 Jun) 623–632.
[188] J. Elbers, C. Hageluken, A. Wadham, Tibolone (Livial®) enhances warfarin-induced anticoagulation in postmenopausal women, Maturitas. 56 (1) (2007 Jan 20) 94–100.
[189] E.H. Ellinwood Jr., M.E. Easler, M. Linnoila, D.W. Molter, D.G. Heatherly, T. D. Bjornsson, Effects of oral contraceptives on diazepam-induced psychomotor impairment, Clin. Pharmacol. Ther. 35 (3) (1984 Mar) 360–366.
[190] J. Ellison, A.J. Thomson, I.A. Greer, I.D. Walker, Drug points: apparent interaction between warfarin and levonorgestrel used for emergency contraception, BMJ. 321 (7273) (2000 Dec 2) 1382.
[191] M. Espir, M.E. Walker, J.P. Lawson, Epilepsy and oral contraception, Br. Med. J. 1 (5639) (1969 Feb 1) 294–295.
[192] B.M. Frey, H.J. Schaad, F.J. Frey, Pharmacokinetic interaction of contraceptive steroids with prednisone and prednisolone, Eur. J. Clin. Pharmacol. 26 (4) (1984) 505–511.
[193] C.L. Garwood, K.A. Van Schepen, R.P. McDonough, A.L. Sullivan, Increased thyroid-stimulating hormone levels associated with concomitant administration of levothyroxine and raloxifene, Pharmacotherapy. 26 (6) (2006 Jun) 881–885.

[194] M. Gringras, G. Beaumont, A. Grieve, Clomipramine and oral contraceptives: an interaction study–clinical findings, J. Int. Med. Res. 8 (Suppl. 3) (1980) 76–80.
[195] M. Grözinger, S. Härtter, C. Hiemke, E.U. Griese, J. Röschke, Interaction of modafinil and clomipramine as comedication in a narcoleptic patient, Clin. Neuropharmacol. 21 (2) (1998 Mar-Apr) 127–129.
[196] S. Gundersen, E. Hannisdal, S. Lundgren, E. Wist, Weekly doxorubicin with or without high-dose medroxyprogesterone acetate in hormone-resistant advanced breast cancer. A randomised study. The Norwegian Breast Cancer Group, Eur. J. Cancer 30A (12) (1994) 1775–1778.
[197] K.C. Gupta, M.Y. Ali, Failure of oral contraceptive with rifampicin, Med. J. Zambia 15 (1) (1980 Dec-1981 Jan) 23.
[198] S. Härtter, A. Nordmark, D.M. Rose, L. Bertilsson, G. Tybring, K. Laine, Effects of caffeine intake on the pharmacokinetics of melatonin, a probe drug for CYP1A2 activity, Br. J. Clin. Pharmacol. 56 (6) (2003 Dec) 679–682.
[199] Health Canada, Important New Safety Information Concerning the Antiepileptic, Lamotrigina, September 27, 2004.
[200] E. Hempel, W. Klinger, Drug stimulated biotransformation of hormonal steroid contraceptives: clinical implications, Drugs. 12 (6) (1976 Dec) 442–448.
[201] J. Hilli, T. Korhonen, M. Turpeinen, J. Hokkanen, S. Mattila, K. Laine, The effect of oral contraceptives on the pharmacokinetics of melatonin in healthy subjects with CYP1A2 g.-163C>A polymorphism, J. Clin. Pharmacol. 48 (8) (2008 Aug) 986–994.
[202] A. Hirsch, J.P. Tillement, J. Chretien, Effets contrariants de la rifampicine sur les contraceptifs oraux: a propos de trois grossesses non desiree chez trois malades, Revue française des maladies respiratoires 2 (1975) 174–182.
[203] R. Jochemsen, M. van der Graaff, J.K. Boeijinga, D.D. Breimer, Influence of sex, menstrual cycle and oral contraception on the disposition of nitrazepam, Br. J. Clin. Pharmacol. 13 (3) (1982 Mar) 319–324.
[204] V.A. John, D.K. Luscombe, H. Kemp, Effects of age, cigarette smoking and the oral contraceptive on the pharmacokinetics of clomipramine and its desmethyl metabolite during chronic dosing, J. Int. Med. Res. 8 (Suppl. 3) (1980) 88–95.
[205] J.V. Joshi, U.M. Joshi, G.M. Sankolli, K. Gupta, A.P. Rao, K. Hazari, U.K. Sheth, B. N. Saxena, A study of interaction of a low-dose combination oral contraceptive with anti-tubercular drugs, Contraception. 21 (6) (1980 Jun) 617–629.
[206] W.J. Jusko, M.J. Gardner, A. Mangione, J.J. Schentag, J.R. Koup, J.W. Vance, Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol, J. Pharm. Sci. 68 (11) (1979 Nov) 1358–1366.
[207] I.E. Kenyon, Unplanned pregnancy in an epileptic, Br. Med. J. 1 (5801) (1972 Mar 11) 686–687.
[208] R.C. Khurana, Estrogen-imipramine interaction, JAMA. 222 (6) (1972 Nov 6) 702–703.
[209] P. Klosterskov Jensen, V. Saano, P. Haring, B. Svenstrup, G.P. Menge, Possible interaction between oxcarbazepine and an oral contraceptive, Epilepsia. 33 (6) (1992 Nov-Dec) 1149–1152.
[210] S.G. Kornstein, M. Toups, A.J. Rush, S.R. Wisniewski, M.E. Thase, J. Luther, D. Warden, M. Fava, M.H. Trivedi, Do menopausal status and use of hormone therapy affect antidepressant treatment response? Findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, J. Women's Health (Larchmt) 22 (2) (2013) 121–131.
[211] K.R. Krishnan, R.D. France, E.H. Ellinwood Jr., Tricyclic-induced akathisia in patients taking conjugated estrogens, Am. J. Psychiatry 141 (5) (1984 May) 696–697.
[212] R. Kropp, Rifampicin und Ovulationshemmer [Rifampicin and oral contraceptives (author's transl)], Prax. Pneumol. 28 (5) (1974 May) 270–272.
[213] I. Kovács, P. Somos, M. Hámori, Examination of the potential interaction between ketoconazole (Nizoral) and oral contraceptives with special regard to products of low hormone content (Rigevidon, Anteovin), Ther. Hung. 34 (3) (1986) 167–170.
[214] K.R. Krishnan, R.D. France, E.H. Ellinwood Jr., Tricyclic-induced akathisia in patients taking conjugated estrogens, Am. J. Psychiatry 141 (5) (1984 May) 696–697.
[215] P.D. Kroboth, R.B. Smith, G.P. Stoehr, R.P. Juhl, Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction, Clin. Pharmacol. Ther. 38 (5) (1985 Nov) 525–532.
[216] R. Kropp, [Rifampicin and oral contraceptives (author's transl)]. [German]. Praxis der Pneumologie vereinigt mit Der Tuberkulosearzt 28, 1974, pp. 270–272.
[217] H. Kutt, F. McDowell, Management of epilepsy with diphenylhydantoin sodium. Dosage regulation for problem patients, JAMA. 203 (11) (1968 Mar 11) 969–972.
[218] Ch. Lafaix, M. Cadoz, A. Richard, P. Pafouillard, L'effet antipilule de la rifampicine, Méd. Hyg. 1181 (1976) 181.
[219] K. Laine, M. Anttila, A. Helminen, H. Karnani, R. Huupponen, Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids, Br. J. Clin. Pharmacol. 47 (3) (1999 Mar) 249–254.
[220] M. LeBel, E. Masson, E. Guilbert, et al., Effects of rifabutin and rifampicin on the pharmacokinetics of ethinylestradiol and norethindrone, J. Clin. Pharmacol. 38 (11) (1998) 1042–1050.
[221] D.K. Luscombe, J. Wright, V.K. Jain, Plasma level studies of clomipramine and desmethylclomipramine following intravenous infusions of clomipramine in depressive patients, Postgrad. Med. J. 53 (Suppl. 4) (1977) 88–96.
[222] L.A. McLintock, A. Dykes, R.C. Tait, I.D. Walker, Interaction between hormone replacement therapy preparations and oral anticoagulant therapy, Br. J. Obstet. Gynaecol. 11088 (2003 Aug) 777–779.
[223] F.P. Meyer, E. Canzler, H. Giers, H. Walther, Zeitverlauf der hemmung der coffeinelimination unter dem einfluß des oralen depotkontrazeptivum Deposiston®, Zentralbl. Gynakol. 113 (6) (1991) 297–302.
[224] J.O. Miners, J. Attwood, D.J. Birkett, Influence of sex and oral contraceptive steroids on paracetamol metabolism, Br. J. Clin. Pharmacol. 16 (5) (1983 Nov) 503–509.
[225] M.C. Mitchell, T. Hanew, C.G. Meredith, S. Schenker, Effects of oral contraceptive steroids on acetaminophen metabolism and elimination, Clin. Pharmacol. Ther. 34 (1) (1983 Jul) 48–53.
[226] D.H. Nelson, H. Tanney, G. Mestman, V.W. Gieschen, L.D. Wilson, Potentiation of the biologic effect of administered cortisol by estrogen treatment, J. Clin. Endocrinol. Metab. 23 (1963 Mar) 261–265.
[227] L. Nocke-Finck, H. Breuer, D. Reimers, Wirkung von Rifampicin auf den Menstruationszyklus und die Ostrogenausscheidung bei Einnahme oraler Kontrazeptiva [Effects of rifampicin on the menstrual cycle and on oestrogen excretion in patients taking oral contraceptives], Dtsch. Med. Wochenschr. 98 (33) (1973 Aug 11) 1521–1523.
[228] S. Palovaara, M. Anttila, L. Nyman, K. Laine, Effect of concomitant hormone replacement therapy containing estradiol and levonorgestrel on the pharmacokinetics of selegiline, Eur. J. Clin. Pharmacol. 58 (4) (2002 Jul) 259–263.
[229] R.V. Patwardhan, P.V. Desmond, R.F. Johnson, S. Schenker, Impaired elimination of caffeine by oral contraceptive steroids, J. Lab. Clin. Med. 95 (1980) 603–608.
[230] P.I. Pillans, M.J. Sparrow, Pregnancy associated with a combined oral contraceptive and itraconazole, N. Z. Med. J. 106 (965) (1993) 436.
[231] C.N. Pisoni, M.J. Cuadrado, M.A. Khamashta, B.J. Hunt, Treatment of menorrhagia associated with oral anticoagulation: efficacy and safety of the levonorgestrel releasing intrauterine device (Mirena coil), Lupus. 15 (12) (2006) 877–880.
[232] B.G. Pollock, M. Wylie, J.A. Stack, D.A. Sorisio, D.S. Thompson, M.A. Kirshner, M. M. Folan, K.A. Condifer, Inhibition of caffeine metabolism by estrogen replacement therapy in postmenopausal women, J. Clin. Pharmacol. 39 (9) (1999) 936–940.
[233] A.J. Prange, Estrogen may well affect the response to antidepressants, JAMA 219 (1972) 143–144.
[234] D.J. Rapport, J.R. Calabrese, Interactions between carbamazepine and birth control pills, Psychosomatics. 30 (4) (1989 Fall) 462–464.
[235] E.C. Rietveld, M.M.M. Broekman, J.J.G. Houben, T.K.A.B. Eskes, J.M. van Rossum, Rapid onset of an increase in caffeine residence time in young women due to oral contraceptive steroids, Eur. J. Clin. Pharmacol. 26 (3) (1984) 371–373.
[236] R.K. Roberts, P.V. Desmond, G.R. Wilkinson, S. Schenker, Disposition of chlordiazepoxide: sex differences and effects of oral contraceptives, Clin. Pharmacol. Ther. 25 (6) (1979 Jun) 826–831.
[237] S.M. Rogers, D.J. Back, P.J. Stevenson, S.F. Grimmer, M.L. Orme, Paracetamol interaction with oral contraceptive steroids: increased plasma concentrations of ethinyloestradiol, Br. J. Clin. Pharmacol. 23 (6) (1987 Jun) 721–725.
[238] A. Sabers, J.M. Buchholt, P. Uldall, E.L. Hansen, Lamotrigine plasma levels reduced by oral contraceptives, Epilepsy Res. 47 (1–2) (2001 Nov) 151–154.
[239] J.J. Schrogie, H.M. Solomon, P.D. Zieve, Effect of oral contraceptives on vitamin K-dependent clotting activity, Clin. Pharmacol. Ther. 8 (5) (1967 Sep-Oct) 670–675.
[240] T. Shelepova, A.N. Nafziger, J. Victory, A.D. Kashuba, E. Rowland, Y. Zhang, E. Sellers, G. Kearns, J.S. Leeder, A. Gaedigk, J.S. Bertino Jr., Effect of a triphasic oral contraceptive on drug-metabolizing enzyme activity as measured by the validated Cooperstown 5+1 cocktail, J. Clin. Pharmacol. 45 (12) (2005 Dec) 1413–1421.
[241] F.E. Sinofsky, S.A. Pasquale, The effect of fluconazole on circulating ethinyl estradiol levels in women taking oral contraceptives, Am. J. Obstet. Gynecol. 178 (2) (1998 Feb) 300–304.
[242] J.L. Skolnick, B.S. Stoler, D.B. Katz, W.H. Anderson, Rifampin, oral contraceptives, and pregnancy, JAMA. 236 (12) (1976 Sep 20) 1382.
[243] S.M. Somani, R.C. Khurana, Mechanism of estrogen-imipramine interaction, JAMA. 223 (5) (1973 Jan 29) 560.
[244] A.E.H. Sonnen, Oxcarbazepine and oral contraceptives, Acta Neurol. Scand. 82 (Suppl. 133) (1990) 37.
[245] G.P. Stoehr, P.D. Kroboth, R.P. Juhl, D.B. Wender, J.P. Phillips, R.B. Smith, Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics, Clin. Pharmacol. Ther. 36 (5) (1984 Nov) 683–690.
[246] A.W. Thomson, C.A. Bonham, A. Zeevi, Mode of action of tacrolimus (FK506): molecular and cellular mechanisms, Ther. Drug Monit. 17 (6) (1995 Dec) 584–591.
[247] K.M. Tornatore, R. Kanarkowski, T.L. McCarthy, M.J. Gardner, A.M. Yurchak, W. J. Jusko, Effect of chronic oral contraceptive steroids on theophylline disposition, Eur. J. Clin. Pharmacol. 23 (2) (1982) 129–134.
[248] E.P. van Puijenbroek, J. Feenstra, R.H. Meyboom, Verstoring van de pilcyclus tijdens het gelijktijdig gebruik van itraconazol en orale anticonceptiva [Pill cycle disturbance in simultaneous use of itraconazole and oral contraceptives], Ned. Tijdschr. Geneeskd. 142 (3) (1998 Jan 17) 146–149.

[249] U. Veronesi, P. Maisonneuve, V. Sacchini, N. Rotmensz, P. Boyle, Italian Tamoxifen Study Group, Tamoxifen for breast cancer among hysterectomised women, Lancet. 359 (9312) (2002 Mar 30) 1122–1124.
[250] M. Rees, R. Angioli, R.L. Coleman, R. Glasspool, F. Plotti, T. Simoncini, C. Terranova, European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis, Maturitas 134 (2020) 56–61.
[251] M. Neves-E-Castro, M. Birkhauser, G. Samsioe, I. Lambrinoudaki, S. Palacios, R. S. Borrego, P. Llaneza, I. Ceausu, H. Depypere, C.T. Erel, F.R. Pérez-López, K. Schenck-Gustafsson, Y.T. van der Schouw, T. Simoncini, F. Tremollieres, M. Rees, EMAS position statement: The ten point guide to the integral management of menopausal health, Maturitas 81 (1) (2015) 88–92.
[252] N. Mendoza, M.D. Juliá, D. Galliano, P. Coronado, B. Díaz, J. Fontes, J.L. Gallo, A. García, M. Guinot, M. Munnamy, B. Roca, M. Sosa, J. Tomás, P. Llaneza, R. Sánchez-Borrego, Spanish consensus on premature menopause, Maturitas 80 (2) (2015) 220–225.

Nicolás Mendoza[a,*], Isabel Ramírez[a], Esther de la Viuda[a], Pluvio Coronado[a], Laura Baquedano[a], Plácido Llaneza[a], Verónica Nieto[a], Borja Otero[a], Sonia Sánchez-Méndez[a], Visitación Álvarez de Frutos[b], Leire Andraca[c], Patricio Barriga[d], Zully Benítez[e], Teresa Bombas[d], Mª. Jesús Cancelo[f], Antonio Cano[g], Camil Castelo Branco[h], Marta Correa[i], José Luis Doval[a], María Fasero[a], Gabriel Fiol[a], Nestor C. Garello[j], Andrea R. Genazzani[h], Ana Isabel Gómez[k], Mª. Ángeles Gómez[a], Silvia González[a], Dimitrios G. Goulis[g], Misericordia Guinot[a], Luis Rolando Hernández[j], Sonia Herrero[l], Eva Iglesias[a], Ana Rosa Jurado[m], Iñaki Lete[a], Daniel Lubián[a], Milagros Martínez[a], Aníbal Nieto[a], Laura Nieto[a], Santiago Palacios[n], Milagros Pedreira[o], Ezequiel Pérez-Campos[a], María Jesús Plá[p], Jesús Presa[a], Francisco Quereda[a], Miriam Ribes[a], Pablo Romero[a], Beatriz Roca[a], Antonio Sánchez-Capilla[q], Rafael Sánchez-Borrego[r], Ana Santaballa[s], Amparo Santamaría[t], Tommaso Simoncini[u], Francisco Tinahones[v], Joaquín Calaf[a]

[a] *Asociación Española para el Estudio de la Menopausia (AEEM), Spain*
[b] *Sociedad Española de Endocrinología y Nutrición (SEEN), Spain*
[c] *Sociedad Española de Farmacia Comunitaria (SEFAC), Spain*
[d] *Red Iberoamericana de Salud Sexual y Reproductiva (REDISSER)*
[e] *Federación Latino Americana de Sociedades de Climaterio y Menopausia (FLASCYM)*
[f] *Sociedad Española de Ginecología y Obstetricia (SEGO), Spain*
[g] *European Menopause and Andropause Society (EMAS)*
[h] *European Society of Gynecology (ESG)*
[i] *Sociedad Española de Contracepción (SEC), Spain*
[j] *Federación Latino-Americana de Sociedades de Obstetricia y Ginecología (FLASOG)*
[k] *Sociedad Española de Senología y Patología Mamaria (SESPM), Spain*
[l] *Sociedad Española de Trombosis y Hemostasia (SETH), Spain*
[m] *Sociedad Española de Médicos de Atención Primaria (SEMERGEN), Spain*
[n] *International Menopause Society (IMS)*
[o] *Sociedad Española de Cardiología (SEC), Spain*
[p] *Sección Ginecología Oncológica de la SEGO, Spain*
[q] *Sociedad Española de Patología Digestiva (SEPD), Spain*
[r] *Fundación Española para el Estudio de la Menopausia (FEEM), Spain*
[s] *Sociedad Española de Oncología Médica (SEOM), Spain*
[t] *Sociedad Española de Hematología y Hemoterapia (SEHH), Spain*
[u] *International Society of Gynecological Endocrinology (ISGE)*
[v] *Sociedad Española de Obesidad (SEED), Spain*

[*] Corresponding author.
E-mail address: nicomendoza@telefonica.net (N. Mendoza).